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References should be limited to those relating directly to the contents of the paper and should be set out in the style outlined by the International Committee of Medical Journal Editors (ICMJE), as shown in the examples below. Additional examples are in the ICMJE sample references. *https://www.nlm.nih.gov/bsd/uniform_requirements.html*

Examples

Article: Rose ME, Huerbin MB, Melick J, Marion DW, Palmer AM, Schiding JK, ***et al***. Regulation of interstitial excitatory amino acid concentrations after cortical contusion injury. Brain Res. 2002;935(1-2):40-6.

Book: Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Book chapter: Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

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Review Article

Effect of early versus late rehabilitation on stroke outcome: Findings from meta-analysis

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Kuwait Medical Journal 2023; 55 (2): 104 - 112

ABSTRACT

Objective: To compare early versus late rehabilitation in terms of quality of life, length of hospital stay and mortality
Design: A systematic search was performed on PubMed, EMBASE and Cochrane Central Register of Controlled Trials.
Setting: Meta-analysis review
Subjects: Compare the effects of early versus late rehabilitation on quality of life, length of hospital stay and mortality
Intervention(s): Findings of several surveys were included and analyzed in this study.
Main outcome measures: Rehabilitation after stroke episode undoubtedly has its beneficial effects. However, when to start rehabilitation (early or late) is a question yet to be answered. Effect of early versus late rehabilitation on quality of life, length of hospital stay and mortality was studied.
Results: Three of five selected studies were cohort and two were observational. Pooled risk ratio was the summary measure for dichotomous variables like Barthel index, recovery rate and mortality. For continuous variables like length of hospital stay, standard mean difference was calculated using random effects model. Heterogeneity coefficient was also calculated for outcome measure.
Conclusion: Early rehabilitation provides better quality of life, short hospital stay and higher survival rate, but the findings were statistically insignificant due to the heterogeneity of studies. Elaborate cohort studies with large sample sizes and long follow up durations are needed to reach a conclusion.

KEY WORDS: early rehabilitation, late rehabilitation, meta-analysis, stroke

INTRODUCTION

Stroke is one of the leading causes of morbidity and mortality worldwide. Every year, a significant number of people are left with residual disabilities ranging from mild to severe; thus hampering day-to-day activities[1-3]. Proper rehabilitation measures commenced at appropriate time can definitely improve both short term as well as long term outcomes, along with enhancing quality of life. The rehabilitation program aims at restoring the affected functions, empowering the person by teaching new ways to perform daily activities, and providing critical education to families on how to look after a stroke survivor[4-6].

Over the past three decades, thousands of randomized controlled trials (RCTs) and cohort studies have been conducted to design and explore various rehabilitation strategies for different stroke outcomes. Systematic reviews and meta-analysis have been conducted to find evidence on which of these rehabilitation strategies perform the best[4,7-11]. However, to conduct a RCT for testing the rehabilitation strategies in itself is a tedious thing. This is because, for a well implemented RCT, it cannot technically be possible to blind the patients as well as the therapist of the intervention. Hence, most of the trials are single blinded studies. Secondly, there are varied outcomes of a stroke. Hence, the rehabilitation strategies are usually tailor made to meet the needs of the patient. So, it gets difficult to test a particular intervention. Thirdly, most of the interventions target to recover a specific body function. So, it is difficult to assess the outcome of intervention in a holistic manner. Therefore, most of the reviews and meta-analysis

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which have been conducted so far focus on exploring the effectiveness of individual interventions, like interventions for improving locomotor function or improving vision or some neurological deficit[11,12]. However, none of the reviews so far have assessed the effect of multiple interventions on overall well-being of a stroke survivor.

The second issue which remains ambiguous in the literature, apart from which type of intervention is better for stroke survivors, is the time period for starting the intervention. Though the studies and experts indicate that the rehabilitation measures should be started as soon as the diagnosis is made and the patient has overcome medical emergency after stroke. A number of trials and studies have been done, but they have initiated rehabilitation measures at varied time periods. A few studies started the interventions as early as within 24 hours[13-15]. On the other hand, a few studies tested the intervention at one week, two weeks, three weeks and even one year after the stroke episode among stroke survivors. Therefore, the effectiveness of rehabilitation intervention would largely vary with varied time periods.

The biggest limitation reported while conducting these studies is the time period that the rehabilitation process was initiated. This is because there are no clear guidelines or consensus on time for initiating the intervention. However, the question of when to start with the rehabilitation process remains unsettled and unanswered in the literature. Hence, the current meta-analysis was conducted with an aim to find out the appropriate time for starting the rehabilitation process after the stroke incident. This study compares the effectiveness of early versus late rehabilitation on stroke outcomes in terms of quality of life and patient survival.

Null hypothesis

There is no difference in the early initiation of rehabilitation measures as compared to late initiation among stroke survivors in terms of quality of life and patient survival rate.

METHODOLOGY

We have done this meta-analysis as per the standard guidelines of Cochrane Collaboration. We used the Preferred Reporting Items for Systematic Reviews and Meta-analyses and Meta-analysis of Observational Studies in Epidemiology to report a systematic review and meta-analysis of RCTs and cohort studies[16].

Study population/ exposure group: First time stroke survivors

Interventions to be compared: Early initiation of rehabilitation versus late initiation of rehabilitation

Outcome measures

1. Quality of life (dependence, restriction of mobility, risk of fall)
2. Survival rate

Operational definitions

Early initiation of rehabilitation: It implies that the rehabilitation was started within seven days of stroke episode (excluding the studies which initiated the rehabilitation within 24 hours of stroke)

Late initiation of rehabilitation: It means that the rehabilitation process was started after 7 days but less than 60 days post stroke episode.

Study selection

We decided to include all RCTs as well as prospective cohort studies which have compared the effectiveness of early vs late initiation of more than one rehabilitation interventions among first time stroke survivors from January 2000 till April 2019.

Inclusion criteria:

1. RCTs and cohort studies with at least 25 study participants in each group
2. Studies which have compared the effect of more than one rehabilitation interventions like locomotor, sensory, cognitive, neurological etc. in combination.
3. Studies which had initiated the intervention within 7 days of stroke (maybe between 24 hours and 3 days or after 3 days or after 5 days but less than 7 days). We have considered this as an early initiation of rehabilitation group.
4. Studies which had initiated the intervention after 7 days of stroke (maybe between 1-2 weeks or at one month or two months but less than 60 days). We have considered this as late initiation of rehabilitation group.

Study selection: The following data sources were searched for all RCTs and prospective cohort- control studies:

a. PubMed,
b. EMBASE/ Excerpta Medica,
c. Cochrane Central Register of Controlled Trials,
d. Google Scholar,
e. Reference lists.

Search strategies were independently designed and performed by two separate investigators. We used the following MeSH terms or keywords in different combinations and permutations for searching studies from January 2000 to April 2019 in advanced PubMed search: "early rehabilitation," "late rehabilitation," "stroke," "hemodiafiltration," "dialysis", "continuous renal replacement therapy" and "slow low efficiency dialysis and its synonyms".

The search strategies described above provided a list of studies. The titles and abstracts of all the retrieved studies were screened independently by two authors. The irrelevant studies were discarded in the first attempt based on inclusion and exclusion criteria. Later on, the full-text version of the shortlisted studies was analyzed for the presence of a measurable outcome variable in terms of:

a. **Quality of life:** We used proxy variables for assessing the quality of life like physical dependence of stroke survivor on caretakers after rehabilitation, restriction of mobility which means how severe was the locomotor disability to hamper the patient mobility after rehabilitation, and risk of fall which implied how well the patient could balance himself to avoid the fall.
b. **Survival rate:** This indicated the number of patients who survived by the end of follow up period out of the total number of patients enrolled for rehabilitation in both the groups.

We did not pose any restrictions on the language of the articles as most of the articles could be translated by the google translate tool; which most of the journals supported for language conversion. However, at the end, we chose only full text articles where detailed data was available for extraction and analysis.

Data extraction

We extracted the following study features: first author, publication year, country, number of participants in each group, renal replacement therapy modalities, number of deaths in each group, number of patients who had 100% kidney recovery, number of patients who were dependent on dialysis after treatment, fluid removal rates in liter/24 hours in both treatment groups, length of stay in intensive care unit (ICU) (days), and clearance rates of serum uric acid, serum creatinine and serum phosphate among two groups. Outcomes reported in two or more articles were extracted for meta-analysis.

Quality assessment of studies

Internal validity of RCTs was assessed using the Cochrane Risk of Bias Tool, while quality of prospective cohort studies were assessed using the Newcastle Ottawa scale.

Data analysis

Extracted data was entered and analyzed by using Revman 5.3. Before the analysis, data were standardized into equivalent units. For dichotomous variables such as mortality, rates in the experimental (SLEDD/ EDD) and control (CRRT) groups were expressed as rate ratio and 95% CI. For continuous variables such as length of ICU stay, fluid removal, and

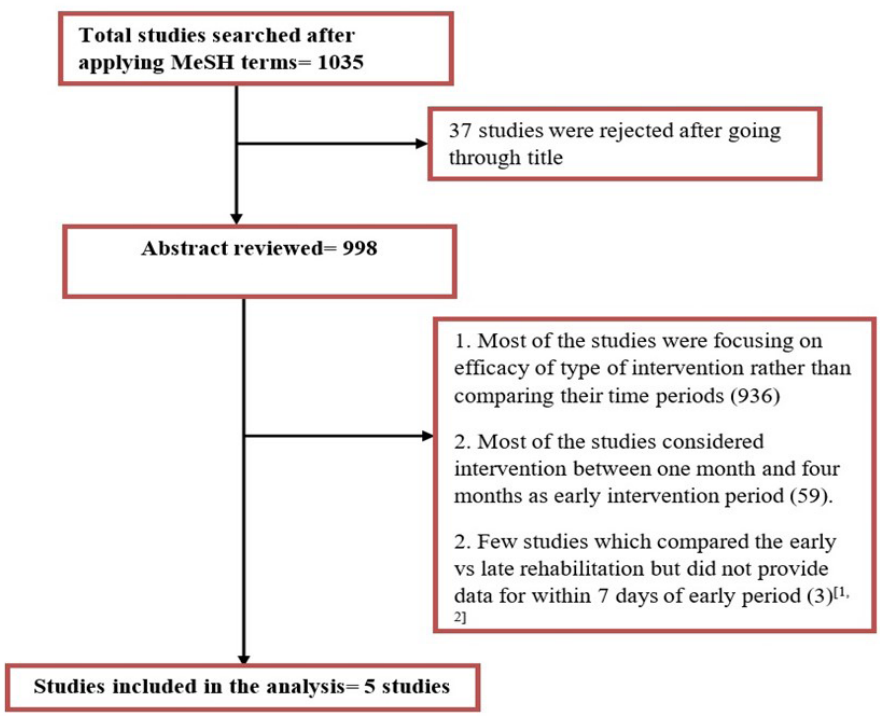

Figure 1: Flowchart showing the selection of studies.

Table 1: Matrix of selected studies

First author, year	Design	Country	Total sample size	Days on which rehab started	Sample size	Mean age	Sex (% males)	Type of rehab	Who administered the rehab	Follow up period
Khasru *et al*, 2017	Prospective cohort	Bangladesh	220	0-24 hours 25-72 hours 4-7 days 8-60 days	25 100 55 40	62.5	52	NA	Physiatrist	3 and 12 weeks
Musicco *et al*, 2003	Cohort	Italy	1716	up to 7 days 8-14 days 15-30 days More than 1 month	515 264 489 448	71.6	50.9	Exercise, occupational, cognitive	NA	At discharge and after 6 months
Nessa *et al*, 2009	Cohort	Bangladesh	48	0-1 week 1-2 weeks 2-3 weeks till 4 weeks	26 12 9 1	NA	NA	Infrared radiation, exercises, speech therapy, occupational, personal care	Physiotherapist	2 weeks
Usman *et al*, 2014	Cross-sectional	Pakistan	100	0-3 days more than 3 days	69 31	NA	61	Mobilization	Physiotherapist	NA
Yagi *et al*, 2017	Retrospective observational study	Japan	1,00,791	0-3 days More than 3	74229 26562	72.8	61.8	Occupational	Neurological specialist, Occupational therapist, speech therapist	NA

biochemical parameters, mean difference and 95% CI were calculated for each study. Heterogeneity in the studies was evaluated using the Cochrane Q test and I^2 statistic to assess the degree of inter study variation. I^2 values of 0% to 24.9%, 25% to 49.9%, 50% to 74.9%, and 75% to 100% were considered as having no, mild, moderate and significant thresholds for statistical heterogeneity.

LITERATURE REVIEW

Some surveys have been conducted in this field throughout the world. Paolucci *et al*[17] examined the effect of early versus delayed inpatient stroke rehabilitation in Italy. They showed that the fast onset–admission interval (OAI) subgroup had significantly higher treatment effectiveness than the medium (P<0.05) and the extended OAI groups (P<0.005). Early intervention was associated with five times greater risk of dropout than delayed treatment. In another survey, Morreale *et al*[18] examined the effects of early versus delayed rehabilitation treatment in hemiplegic patients with ischemic stroke. They reported that Barthel Index significantly changed between early versus delayed groups at 12 months (P=0.01). Motricity index in both upper (P=0.01) and lower limbs (P=0.001) and six-minute walking test (P=0.01) increased in early versus delayed groups regardless of rehabilitation schedule. They revealed that the rehabilitation technique did not affect long term motor recovery. Tong *et al*[19] reported that post-stroke rehabilitation at 48 hours might be helpful. Very early intensive mobilization did not lead to a favorable outcome at 3 months. Langhorne *et al*[20] stated that very early mobilization did not increase the number of people who survived or made a good recovery after stroke. Additionally, very early mobilization may reduce the length of stay in the hospital. However, results from the single largest trial and an analysis of trials that started mobilizing participants very early raised the concern that starting intensive mobilization within 24 hours of a stroke may carry some increased risk, at least for some people with stroke. This potential risk needs to be clarified.

Overall, trials of rehabilitation in the first two weeks after stroke are scarce. In the realm of very early mobilization, one large and one small trial found potential harm from mobilizing patients within the first 24 hours after stroke, and only one small trial found benefit in doing so. For the upper extremity, constraint-induced movement therapy appears to have benefit when started within 2 weeks of stroke. Evidence for non-invasive brain stimulation in the acute period remains scant and inconclusive. For aphasia, the evidence is mixed, but intensive early therapy might benefit patients with severe aphasia. Mirror therapy that began early after stroke shows promise for the alleviation of neglect. Novel approaches to treating dysphagia early after stroke appear promising, but the high rate of spontaneous improvement makes their benefit challenging to gauge[21].

RESULTS

Study selection

The combined literature search identified around 1035 studies which contained the MeSH terms either in the title or abstract. After reviewing the title, we included 998 studies for abstract review. Finally, only five studies matched the inclusion criteria[22-26]. We decided to include the following types of studies in our review:

1. Studies providing data or which have compared the early intervention (within 7 days) with late intervention (more than 7 days but less than 60 days).
2. Studies which provided more than one type of rehabilitation to the stroke survivors.

The excluded studies were rejected on various grounds described in Figure 1. The eligible studies were conducted between years 2003 and 2017. Out of the five eligible studies, three were cohort studies[23-25] and two were observational ones carried out among different parts of the world, as depicted in Table 1[22,26].

The total population covered was 1,02,875. Of these, 27,856 (27%) individuals were rehabilitated after a period of seven days post stroke but the rest were rehabilitated within 7 days of stroke. The mean age of study participants varied from 62 to 74 years.

Assessment of methodological quality

Newcastle Ottawa scale was used to assess bias among observational and cohort study as presented in Table 2. It was assessed that selection and allocation of exposure to both groups was well defined in all the studies. However, only two studies had analyzed the data both age- and sex-wise. Follow up period was mentioned in three studies only. Of these three studies, only two studies had an adequately long follow up period.

Outcome 1: Length of hospital stay

The summary mean difference of selected studies indicated that there was no significant difference in the mean days of hospital stay as shown in Table 3[24, 26]. The heterogeneity among the studies was found to be 100% (mean difference= -123.77, 95% CI= -273.76 to 26.21, *P*=0.11) (Figure 2).

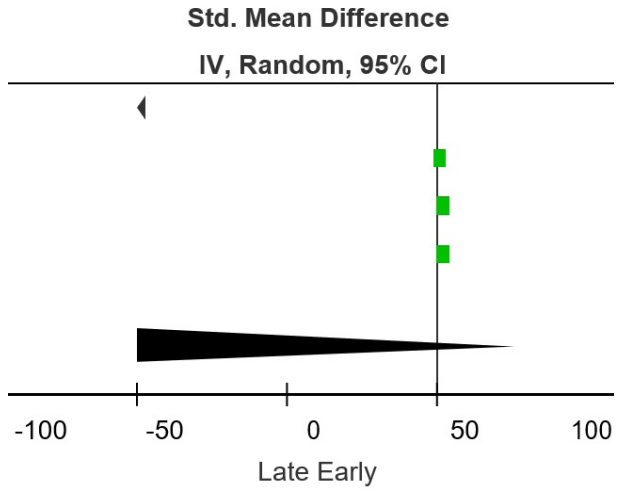

Figure 2: Length of hospital stay among two groups of stroke patients.

Outcome 2: Restricted mobility

This meta-analysis showed that there was no significant difference in the number of stroke patients having restricted mobility between those who were rehabilitated within seven days and those who were rehabilitated after 7 days[23]. The heterogeneity was found to be 8% among the selected studies as depicted in Table 4 and Figure 3 [RR=1.15 (0.75-1.74), *P*=0.52].

Outcome 3: Difference in Barthel index

This meta-analysis showed that there was no significant difference in the Barthel index (quality of life) between patients who were rehabilitated within seven days and those who were rehabilitated after 7 days[23,26]. The heterogeneity was found to be 83% (very high) among the selected studies as depicted in Table 5 and Figure 4 [RR=8.18 (0.51-130.90), *P*=0.14].

Table 2: Bias matrix for prospective cohort studies

Parameters of NOS scale	Musicco *et al*, 2003	Nessa *et al*, 2009	Usman *et al*, 2014	Khasru *et al*, 2017	Yagi *et al* 2017
Representatives of exposed cohort	Low	Low	Low	Low	Low
Selection of non- exposed cohorts	Low	Low	Low	Low	Low
Ascertainment of exposure	Low	Low	Low	Low	Low
Outcome of interest not present	Low	Low	Low	Low	Low
Comparability of cohort (age-wise)	Low	High	High	High	Low
Comparability of cohort (severity of illness wise)	Low	High	High	High	Low
Assessment of outcome	Low	Low	High	High	Low
Was follow-up long enough	Low	Low	High	Low	High
Adequacy of follow up of cohorts	Low	Low	High	High	High

NOS: Newcastle Ottawa scale

Table 3: Length of hospital stay among two groups of stroke patients

Study or subgroup	Early			Late			Std. Mean Difference	
	Mean	SD	Total	Mean	SD	Total	Percentage	IV, Random, 95% CI
Yagi *et al*, 2017 (0-3 days vs more than 1 week)	19	0.01	74,229	24	0.01	26,562	25	-500.00 [-502.18, -497.81]
Nessa *et al*, 2009 (0-1 week vs 1-2 weeks)	87.89	22.04	26	67	18.97	12	25	0.97 [0.25, 1.69]
Nessa *et al*, 2009 (0-1 week vs 2-3 weeks)	87.89	22.04	26	47.67	12.68	9	25	1.95 [1.05, 2.85]
Nessa *et al*, 2009 (0-1 week vs 3-4 weeks)	87.89	22.04	26	43	0.01	1	25	1.98 [-0.10, 4.05]
Total (95% CI)			74,307			26,584	100	-123.77 [-273.76, 26.21]

Heterogeneity: Tau² = 23422.60; Chi² = 190871.14, df = 3
Test for overall effect: Z = 1.62 (*P* = 0.11)
(*P*<0.00001); I² = 100%

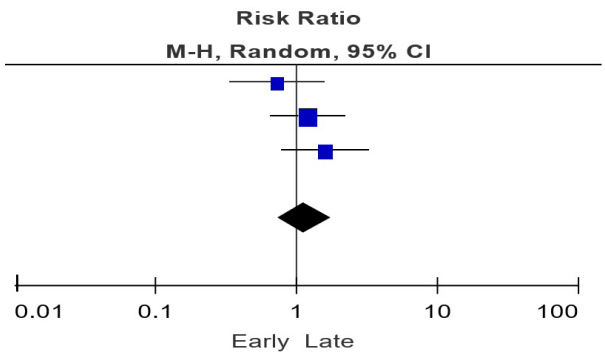

Figure 3: Difference in mobility before and after rehabilitation between early and late rehabilitation groups.

Outcome 4: Full recovery rate

This meta-analysis showed that there was no significant difference in the full recovery rate of patients between those who were rehabilitated within seven days and those who were rehabilitated after 7 days[22,23]. The heterogeneity was found to be high (76%) among the selected studies as depicted in Table 6 and Figure 5 [RR=1.29 (0.60-2.76), *P*=0.52].

Outcome 5: Survival rate

This meta-analysis showed that there was no significant difference in the survival rate of patients between those who were rehabilitated within seven days and those who were rehabilitated after 7 days[23,24]. The heterogeneity was found to be 0% among the selected studies as depicted in Table 7 and Figure 6 [RR=1.00 (0.98-1.03), *P*=0.83, I²=0%].

DISCUSSION

We conducted this meta-analysis and identified five original studies that compared the effects of early rehabilitation and late rehabilitation among 1,02,875 stroke survivors in terms of length of hospital stay, quality of life, mobilization after stroke and their survival. We found that there was no significant

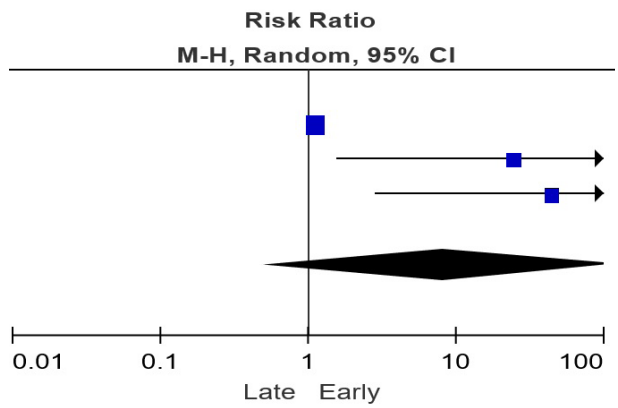

Figure 4: Barthel index among two groups.

Table 4: Difference in mobility before and after rehabilitation between early and late rehabilitation groups

Study or subgroup	Late		Early			Risk Ratio
	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
Khasru *et al*, 2017 (4-7 days vs 8-60 days)	10	55	10	40	27.1%	0.73 [0.33, 1.58]
Khasru *et al*, 2017 (25-72 hours vs 8-60 days)	30	100	10	40	41.7%	1.20 [0.65, 2.22]
Khasru *et al*, 2017 (0-24 hours vs 8-60 days)	10	25	10	40	31.2%	1.60 [0.78, 3.29]
Heterogenicity: Tau²= 0.01; Chi²= 2.17, df= 2 (*P*= 0.34), I²= 8%						
Test for overall effect" Z = 0.64 (*P*= 0.52)		180		120	100.0%	1.15 [0.75, 1.74]
Total (95% CI)	50		30			
Total events						

Table 5: Barthel index among two groups

Study or subgroup	Early event	Total	Late event	Total	Weight	Risk ratio M-H, Random, 95% CI
Khasru *et al*, 2017 (0-24 hours vs 8-60 days)	0	25	0	40		Not estimable
Yagi *et al*, 2017 (0-3 days vs more than 1 week)	33,013	74,229	10,600	26,562	41.4%	1.11 [1.10, 1.13]
Khasru *et al*, 2017 (25-72 hours vs 8-60 days)	30	100	0	40	29.3%	24.76 [1.55, 395.48]
Khasru *et al*, 2017 (4-7 days vs 8-60 days)	30	55	0	40	29.3%	44.66 [2.81, 709.34]
Total (95% CI)						
Total events	33,073	74,409	10,600	26,682	100.0%	8.16 [0.51, 130.90]

Heterogenicity: Tau²= 4.85; Chi²= 11.72, df= 2 (*P*= 0.03), I²= 83%
Test for overall effect: Z = 1.48 (*P*= 0.14).

difference for these parameters among the two groups. However, the measure of effect, *i.e.* risk ratios for Barthel index, mobility restriction and survival rates were better among stroke patients whose rehabilitation was started within a week after the stroke episode as compared to the late group.

This finding may be attributed to a number of factors both related to individual studies as well as process of meta-analysis. The first reason is that all the studies included in the analysis have described the effectiveness of early vs late rehabilitation in terms of varied outcome measures. That's why, in spite of limiting the number of outcomes for the meta-analysis, only 2-3 studies out of five described the outcome of interest[22-26]. This in turn reduces the total sample size for the summary measures in meta-analysis. The

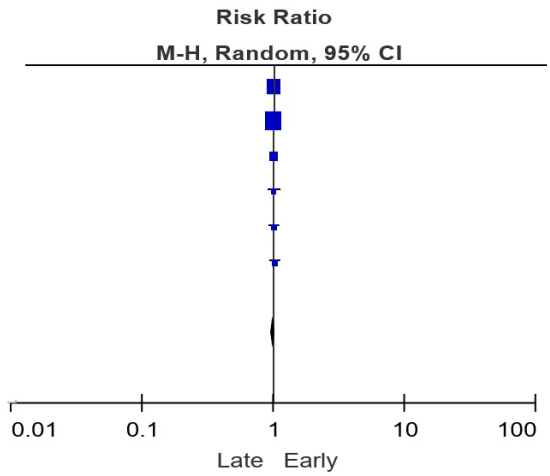

Figure 6: Survival rate of stroke patients between early vs late rehabilitation groups.

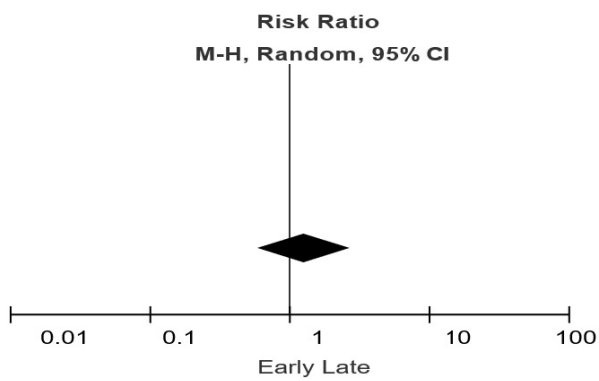

Figure 5: Full recovery rate among two groups.

second reason is the small sample size of individual studies as mentioned in Table 6. The third reason is the high heterogeneity among individual studies due to varied geographical distributions, different types of rehabilitation modalities given for varied time periods, difference in the type of setting or personnel who administered the rehab and also, difference in the type of stroke for which rehab was given. The fourth reason is the presence of bias in individual studies as depicted in Table 7. All these factors influence the effect size of the study and in turn, the summary measure in the analysis, which leads to insignificant findings in the meta- analysis.

Table 6: Full recovery rate among two groups

Study or subgroup	Early event	Total	Late event	Total	Weight	Risk ratio M-H, Random, 95% CI
Khasru *et al*. 2017 (4-7 days vs 8-60 days)	5	55	10	40	21.3%	0.36 [0.13, 0.98]
Khasru *et al*. 2017 (25-72 hours vs 8-60 days)	30	100	10	40	27.5%	1.20 [0.65, 2.22]
Khasru *et al*. 2017 (0-24 hours vs 8-60 days)	10	25	10	40	25.8%	1.60 [0.78, 3.29]
Usman *et al*. 2014 (0-3 days vs more than one week)	43	69	6	31	25.4%	3.22 [1.53, 6.76]
Total (95% CI)		249		151	100.0%	1.29 [0.60, 2.76]
Total events	88		36			

Heterogeneity: Tau² = 0.45; Chi² = 12.32, df = 3 (*P* = 0.006); I² = 76%
Test for overall effect: Z = 0.65 (*P* = 0.52)

Table 7: Survival rate of stroke patients between early vs late rehabilitation groups

Study or subgroup	Early event	Total	Late event	Total	Weight	Risk ratio M-H, Random, 95% CI
Khasru *et al*, 2017 (4-7 days vs 8-60 days)	55	55	40	40	30.5%	1.00 [0.96, 1.04]
Khasru *et al*, 2017 (25-72 hours vs 8-60 days)	100	100	40	40	40.3%	1.00 [0.96, 1.04]
Khasru *et al*, 2017 (0-24 hours vs 8-60 days)	25	25	40	40	13.4%	1.00 [0.94, 1.07]
Musicco *et al*, 2003 (7 days vs 8-14 days)	326	515	166	264	4.2%	1.01 [0.90, 1.13]
Musicco *et al*, 2003 (7 days vs 15-30 days)	326	515	305	489	6.0%	1.01 [0.92, 1.12]
Musicco *et al*, 2003 (7 days vs more than one month)	326	515	277	448	5.6%	1.02 [0.93, 1.13]
Total (95% CI)						
Total events	1158	1725	868	1321	100.0%	1.00 [0.98, 1.03]

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.15$, df = 5 ($P = 0.95$); $I^2 = 0\%$
Test for overall effect: Z = 0.21 ($P = 0.83$)

The second part of the discussion is based on the novel methodology we have used to analyse the data in this analysis, which may be considered a strength of this type of meta-analysis. Here, there has been an age long unsettled debate on deciding the cut-off to define early and late rehabilitation. For instance, Bernhardt *et al* and Indrevik *et al* considered early rehabilitation to be within 24 hours of the stroke episode. Similarly, Kelly-Hayes suggested the cut-off of less than 72 hours to be early, Cifu considered early to be within 3-30 days and Teasell mentioned it to be less than 30 days[27,28]. However, the recent guidelines suggest that as soon as the patient gets stabilized from stroke and is out of life threatening episode, the rehabilitation must begin[29]. Hence, a few researchers like Bernhardt *et al* planned RCTs exploring the effect of intensive rehabilitation within 24 hours as very early vs late rehabilitation, and it was concluded that very early rehabilitation within 24 hours could actually harm the recovery of the patient instead of speeding up the rehabilitation. Hence, we decided to exclude the studies which implemented rehabilitation within 24 hours and decided to include the studies considering early rehabilitation period from more than 24 hours but less than 7 days. Any rehabilitation that was started between 7 days to 60 days was treated as late rehabilitation period.

The next problem we faced during data extraction was the varied time periods in individual studies for which they presented the data, as shown in Table 6. In the absence of raw data from the individual studies, we decided to consider the different time periods in one study as different data readings and compared it with late rehabilitation period. Though this new methodology diluted the effect of early rehabilitation, it helped us to utilize the existing data also. For instance, Nessa *et al* presented his findings as per four weeks (0-1 week, 1-2 week, 2-3 weeks and 3-4 weeks) when the patient was enrolled[25]. Here, we compared the findings of 0-1 week (early rehabilitation period as per operational definition) with all other three readings at 1-2 week, 2-3 weeks and 3-4 weeks individually. This way we tried to utilize the maximum data available. Otherwise, there is no other way that the quantitative analysis of such behavioral studies can be summarized in the absence of a standardized methodology followed by different authors. This is one reason why all the meta-analysis conducted in the past are systematic reviews with qualitative findings, as recently done by Coleman *et al*[5].

The studies which assess the outcome measures like quality of life or recovery status of an individual are not purely quantitative studies. In these studies, the authors try their best to quantify a subjective viewpoint or a qualitative measure like quality of life. Hence, it is natural or innate to have methodological differences between studies. That's the reason that the meta-analysis conducted in the past focus on comparing the effectiveness of rehabilitation strategies on one aspect, like motor or dysphagia etc[9,10]. However, none of them have attempted to summarize the findings of qualitative parameters like quality of life and recovery rate among much disputed early and late rehabilitation periods till date. This is a first of its type meta-analysis with novel methodology, which can be considered as its strength.

CONCLUSION

Hence, future research should focus on well-planned cohort studies with longer duration of follow up, along with addressal on key outcome measures like quality of life as measured by Barthel Index and mortality rates, by taking into account standard definition of early and late period of rehabilitation.

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Conflict of interest: None

REFERENCES

1. Salter K, Jutai J, Hartley M, Foley N, Bhogal SK, Bayona N, *et al*. Impact of early vs delayed admission to rehabilitation on functional outcomes in persons with stroke. J Rehabil Med 2006; 38(2):113-7.
2. Yildiz S, Savas S, Akkus S, Soyupek FC, Ilgun E. Impact of delayed initiation to stroke rehabilitation on functional outcomes and medical complications. Turk J Physical Med Rehabilitation 2007; 53(2):45-9.
3. Gorelick PB. The global burden of stroke: persistent and disabling. Lancet Neurol 2019; 18(5):417-8.
4. Ada L, Mackey F, Heard R, Adams R. Stroke rehabilitation: does the therapy area provide a physical challenge? Aust J Physiother 1998; 44(1):33-8.
5. Coleman ER, Moudgal R, Lang K, Hyacinth HI, Awosika OO, Kissela BM, *et al*. Early rehabilitation after stroke: a narrative review. Curr Atheroscler Rep 2017; 19(12):59.
6. Zheng H, Cao N, Yin Y, Feng W. Stroke recovery and rehabilitation in 2016: a year in review of basic science and clinical science. Stroke Vasc Neurol 2017; 2(4):222-9.
7. Mweshi M, Shula H, Nkhata L, Chiluba BC. The best time to start stroke rehabilitation: A review of the evidence in resource-adequate and resource constrained settings. J Prevent Rehabilitative Med 2016; 1(1):7-12.
8. Rosewilliam S, Roskell CA, Pandyan AD. A systematic review and synthesis of the quantitative and qualitative evidence behind patient-centred goal setting in stroke rehabilitation. Clin Rehabil 2011; 25(6):501-14.
9. Stinear C, Ackerley S, Byblow W. Rehabilitation is initiated early after stroke, but most motor rehabilitation trials are not: a systematic review. Stroke 2013; 44(7):2039-45.
10. Takeuchi N, Izumi S-I. Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity. Stroke Res Treat 2013; 2013:128641.
11. Foley N, Hussein N, Saikaley M, Iruthayarajah J, Wiener J, Speechley M, *et al*. The elements of stroke rehabilitation. Evidence-Based Rev Stroke Rehabilitation 2007.
12. Krakauer JW, Carmichael ST, Corbett D, Wittenberg GF. Getting neurorehabilitation right: what can be learned from animal models? Neurorehabil Neural Repair 2012; 26(8):923-31.
13. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A very early rehabilitation trial for stroke (AVERT) phase II safety and feasibility. Stroke 2008; 39(2):390-6.
14. Cumming TB, Thrift AG, Collier JM, Churilov L, Dewey HM, Donnan GA, *et al*. Very early mobilization after stroke fast-tracks return to walking: further results from the phase II AVERT randomized controlled trial. Stroke 2011; 42(1):153-8.
15. Langhorne P, Stott D, Knight A, Bernhardt J, Barer D, Watkins C. Very early rehabilitation or intensive telemetry after stroke: a pilot randomised trial. Cerebrovascular Dis 2010; 29(4):352-60.
16. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8(5):336-41.
17. Paolucci S, Antonucci G, Grasso MG, Morelli D, Troisi E, Coiro P, *et al*. Early versus delayed inpatient stroke rehabilitation: a matched comparison conducted in Italy. Arch Phys Med Rehabil 2000; 81(6):695-700.
18. Morreale M, Marchione P, Pili A, Lauta A, Castiglia SF, Spallone A, *et al*. Early versus delayed rehabilitation treatment in hemiplegic patients with ischemic stroke: proprioceptive or cognitive approach? Eur J Phys Rehabil Med 2016; 52(1):81-9.
19. Tong Y, Cheng Z, Rajah GB, Duan H, Cai L, Zhang N, *et al*. High intensity physical rehabilitation later than 24 h post stroke is beneficial in patients: a pilot randomized controlled trial (RCT) study in mild to moderate ischemic stroke. Front Neurol 2019; 10:113.
20. Langhorne P, Collier JM, Bate PJ, Thuy MN, Bernhardt J. Very early versus delayed mobilisation after stroke. Cochrane Database Syst Rev 2018; 10(10):CD006187.
21. Coleman ER, Moudgal R, Lang K, *et al*. Early rehabilitation after stroke: a narrative review. Cur Atherosclerosis Reports 2017;19(12):1-2.
22. Khan MU, Sami N, Khan AS, Danish SH, Ahmad F. To compare the effects of early and late mobilization in post stroke patients. J Med Res 2014; 3:49-53.
23. Khasru MR, Salek A, Moniruzzaman M, Marzen T, Haseen F, Siddiq AB, *et al*. Early versus late rehabilitation for stroke survivors: A prospective study. Bangabandhu Sheikh Mujib Med Univ J 2017; 10(4):204-9.
24. Musicco M, Emberti L, Nappi G, Caltagirone C; Italian Multicentre Study on Outcomes of Rehabiliation of Neurological Patients. Early and long-term outcome of rehabilitation in stroke patients: the role of patient characteristics, time of initiation, and duration of interventions. Arch Phys Med Rehabil 2003; 84(4):551-8.
25. Nessa J, Khaleque MA, Begum S, Ahmed AH, Islam S, Afsan M. Rehabilitation of stroke patients-Effects of early intervention of physical therapy on functional outcome. Bangl J Anatomy 2009; 7(1):62-7.
26. Yagi M, Yasunaga H, Matsui H, Morita K, Fushimi K, Fujimoto M, *et al*. Impact of rehabilitation on outcomes in patients with ischemic stroke: a nationwide retrospective cohort study in Japan. Stroke 2017; 48(3):740-6.
27. Cifu DX, Stewart DG. Factors affecting functional outcome after stroke: a critical review of rehabilitation interventions. Arch Phys Med Rehabil 1999; 80(5 Suppl 1):S35-9.
28. Kelly-Hayes M, Beiser A, Kase CS, Scaramucci A, D'Agostino RB, Wolf PA. The influence of gender and age on disability following ischemic stroke: the Framingham study. J Stroke Cerebrovasc Dis 2003; 12(3):119-26.
29. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, *et al*. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2016; 47(6):e98-e169.

Original Article

Serum ischemia modified albumin level in the differential diagnosis of acute appendicitis and non-specific abdominal pain of children

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ABSTRACT

Objectives: To investigate the role of the ischemia modified albumin (IMA) and the IMA/albumin ratio (IMA/AlbR) in the differential diagnosis of acute appendicitis (AA) in children applying to the emergency service due to the complaint of abdominal pain
Design: Prospective study
Setting: The study was conducted in the pediatric emergency department of a tertiary care hospital.
Subjects: Children with abdominal pain
Interventions: The patients were separated into two groups; AA and non-specific abdominal pain (NSAP) groups. White blood cell (WBC), neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), IMA and IMA/AlbR levels were compared between the two groups and the receiver operating characteristic (ROC) analysis was performed.
Main outcome measures: AA patients had a differential diagnosis based on NSAP
Results: It was found that WBC, NLR, CRP, IMA, and IMA/AlbR results were significantly higher in AA group than NSAP group. According to the ROC analysis, the cut-off value was 0.777 AbsU for IMA and 16.71% for IMA/AlbR, in distinguishing the patients in AA group from those in NSAP group. When IMA or IMA/AlbR was included into any of WBC, NLR and CRP tests, the sensitivity and specificity values were found to be 87.5% and 88.9% for WBC-IMA, 80.9% and 84.2% for WBC-IMA/AlbR, 100% and 84.2% for NLR-IMA, 80.9% and 84.2% for NLR-IMA/AlbR, 71.4% and 96% for CRP-IMA, and 27.7% and 95.8% for the CRP-IMA/AlbR.
Conclusion: When IMA and IMA/AlbR parameters were added to the WBC, NLR and CRP tests in differential diagnosis of AA patients from NSAP patients, sensitivity and specificity in particular increased significantly.

KEY WORDS: acute appendicitis, IMA, IMA/Albumin ratio, non-specific abdominal pain

INTRODUCTION

Acute abdominal pain is a common symptom encountered both in children and adults who apply to the emergency room and usually in the intra-abdominal area, and rarely in the extra-abdominal area. Acute abdominal pain is categorized as urgent and non-urgent. The most frequent reasons for visiting the emergency department include acute appendicitis (AA), acute diverticulitis and intestinal obstruction. Being the most frequent pathology requiring urgent surgery, AA is one of the most frequent and important reasons for acute abdominal pain in children. On the other hand, non-emergency reasons generally include non-specific abdominal pain (NSAP) and digestive system diseases[1-3].

The most common reason for children undergoing emergency surgery is AA. The diagnosis of AA is initially established based on clinical findings. However,

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it can be more difficult to diagnose children with AA because one out of three AA cases do not exhibit typical clinical or lab findings[2]. White blood cell (WBC), neutrophil ratio, C-reactive protein (CRP), abdominal ultrasound and computerized tomography may help in diagnosing AA, but none of them is adequate in terms of final or differential diagnosis of surgical and non-surgical acute abdomen. Late diagnosis can lead to complications and even death. When considering the correlation between late diagnosis and increased complication rates, certain subsidiary tests that could pave the way for early diagnosis are needed[4-8].

Serum albumin transforms into ischemia modified albumin (IMA) and develops as a result of the decreased bonding capacity for cobalt, copper and nickel, by being altered on the N-terminal end due to oxidative stress or ischemia. Serum IMA levels have been found to be higher than those of the control group for several diseases, including acute coronary syndrome, pulmonary emboli, cerebrovascular disease, peripheral vascular disorder and mesenteric ischemia[9,10].

There are a limited number of studies indicating that IMA levels increase in AA. However, there is no study in the literature comparing NSAP and AA. It is thought that IMA levels would increase in the AA compared to the NSAP. The aim of this study was to assess IMA levels and IMA/Albumin Ratio (IMA/AlbR) of children with AA or NSAP, who applied to the emergency room due to the complaint of abdominal pain, and to investigate the role of these parameters in the differential diagnosis of AA.

MATERIALS AND METHODS

The study was conducted between April and July 2019. Seventy-two patients (M:36, F:36) who were aged 2 to 17 years (mean±SD: 10.29±3.99), were brought to the pediatric emergency department due to the complaint of abdominal pain on their right lower quadrant, were included in the study. The children's parents were informed about the study and asked to sign an informed consent form and then the children were included in the study. Detailed anamnesis and physical examinations were performed on all of these children. Necessary routine examination and treatment procedures were performed on these patients in the emergency department. The sample group was separated into two groups; AA and NSAP. In AA group, the patients were diagnosed with AA approved with pathology and were operated as a result of routine procedures (n=36, M:18, F:18). In the NSAP group, the patients were brought to the emergency service due to the complaint of right lower quadrant pain and were not operated because AA was not considered (n=36, M:18, F:18). All the data of the AA and NSAP groups (such as age, gender, laboratory examinations, radiological examinations, etc.) were received from patient files. Children who had any chronic systemic disease, chronic abdominal pain, drug use, history of any surgical operation, urinary tract infection, neurological disorder, diabetes mellitus and psychiatric disorder and had undergone an appendectomy operation before were not included in the study. Ethics committee approval was obtained from the Ethics Committee of KTO Karatay University Medical Faculty (Decision date: 10/01/2019, Decision no: 2019/004).

In the study, 5 mL venous blood samples taken from both groups were placed into standard biochemistry tubes (with gel and vacuum). The samples were centrifuged at 3000g for ten minutes and their supernatants were separated. The serum samples separated were kept at -80 °C until the study day. Among the samples, serum albumin and IMA levels were examined and the IMA/AlbR (IMA/AlbR= IMA / Alb*100) was calculated[11].

Albumin and IMA measurement

Serum albumin level (albumin commercial kit, Beckman Coulter Inc., Brea, CA) was measured using the Olympus AU 400 (Olympus life & Material Science Europe, Hamburg, Germany) autoanalyzer. Serum IMA levels were determined by albumin cobalt binding test, a rapid colorimetric method developed by Bar-Or *et al*[12]. According to this method, 120 μL of cobalt dichloride reagent was added into 35 μL of serum and incubated for five minutes. During this incubation period, cobalt binds to the N-terminal of unmodified albumin. When 35 μL of dithiothreitol reagent was added, dithiothreitol combined with unbound cobalt, and resulted in color development. Color change of the sample was evaluated at 480 nm and the values were measured in absorbance units (AbsU).

Statistical analysis

The data were analyzed using the SPSS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and MedCalc (Trial Version, MedCalc Software, Belgium) statistical package programs. The variables were evaluated after controlling the prerequisites of normality and variance homogeneity (Shapiro Wilk and Levene's Test). In the data analysis, differences between the two dependent groups were evaluated using the independent samples test. If the prerequisites of the parametric test were not provided, the Mann-Whitney U Test was used. Mean±standard deviation and median±interquartile range (IQR), percentage and frequency values were used for the variables. In the correlation analysis, the Pearson's correlation was performed for the parametric

tests and the Spearman's correlation analysis was performed for the non-parametric tests. The receiver operating characteristic (ROC) curve analysis was performed to evaluate the clinical power of markers in predicting appendicitis. The cut-off value was determined using the Youden's index (J=sensitivity+ specificity −1), which coincides with the point closest to the upper left corner in the ROC diagram and reflects the highest total sensitivity and specificity. The value of $P<0.05$ was accepted as significance level of the tests.

RESULTS

A total of 72 participants (M:36, 50% - F:36, 50%) aged between 2 and 17 years and having an age average of 10.24±4.00 years were included into the study. While 36 children (M:18, F:18) having an age average of 10.53±3.49) years were assigned to the AA group, 36 children (M:18, F:18) having an age average of 9.96±4.48 years were assigned to the NSAP group. It was determined that there was no statistically significant difference between the groups in terms of age, gender and serum albumin values ($P>0.05$, independent samples test).

Upon comparison of the WBC values of the participants, it was determined that AA group had statistically significantly higher WBC (mean±SD: 15.73±4.35) values than the NSAP group (12.41±5.29) ($P=0.005$, independent samples test). Upon comparison of the neutrophil-lymphocyte ratio (NLR) and CRP values of both groups, it was found that AA group had statistically significantly higher NLR (median±IQR: 6.52±5.33) and CRP (median±IQR: 18.25±68.20) values compared to NSAP group, whose NLR and CRP values were 3.20±5.95 and 3.92±11.82, respectively ($P=0.002$, Mann-Whitney U test, for both groups). When the IMA and IMA/AlbR values of both groups were compared, it was determined that IMA (mean±SD: 0.752±0.154) and IMA/AlbR (mean±SD: 16.84±4.05) values of AA group were statistically significantly higher than IMA (0.685±0.127) and IMA/AlbR (14.95±2.98) values of NSAP group (respectively, $P=0.048$ and $P=0.028$, independent samples test). Table 1 shows age, WBC, NLR, CRP, IMA, albumin and IMA/AlbR values of both AA and NSAP groups.

ROC analysis was used to distinguish the patients in AA group from those in NSAP group for WBC, NLR, CRP, IMA and IMA/AlbR. The results of ROC analysis indicated that these values were significant and the cut-off value was 11.820 /mm^3 (sensitivity: 80.56%, specificity: 61.11% and area under the curve (AUC): 0.707) for WBC, 3.55% (94.44%, 58.33% and 0.711) for NLR, 20.7 mg/L (50%, 86.11% and 0.709) for CRP, 0.777 AbsU (52.78%, 77.78% and 0.645) for IMA and 16.71% (55.56%, 75% and 0.647) for IMA/AlbR when it came to distinguishing patients in AA group from those in NSAP group. Table 2 shows the ROC analysis results for WBC, NLR, CRP, IMA and IMA/AlbR. Figure 1 shows the ROC analysis diagram for IMA and IMA/AlbR.

Table 1: Age, WBC, NLR, CRP, IMA and IMA/AlbR values of Acute Appendicitis (AA) and Non-Specific Abdominal Pain groups (NSAP).

Age, WBC, NLR, CRP, IMA, and IMA/AlbR values of AA and NSAP groups	Acute Appendicitis n=36 (M:18, F:18)	Non-Specific Abdominal Pain n=36 (M:18, F:18)	*P*-value
Age (year)*	10.53 (±3.49)	9.96 (±4.48)	0.550#
WBC (1000/mm^3)*	15.73 (±4.35)$^{\alpha}$	12.41 (±5.29)	0.005#
NLR (%)**	6.52 (±5.33)$^{\alpha}$	3.20 (±5.95)	0.002¥
CRP (mg/L)**	18.25 (±68.20)$^{\alpha}$	3.92 (±11.82)	0.002¥
IMA (AbsU)*	0.752 (±0.154)$^{\alpha}$	0.685 (±0.127)	0.048#
IMA/AlbR (%)*	16.84 (± 4.05)$^{\alpha}$	14.95 (±2.98)	0.028#

*:values are given as mean(±sd),**:values are given as Median(±IQR), # *P* value for Independent Samples Test.¥ *P* value for Mann-Whitney U Test, α: Statistically significantly different from the control group, sd:Std. Deviation, IQR: Interquartile Range, WBC:White blood cell, NLR: Neutrophile Lymphocyte Ratio, CRP: C-reactive protein, IMA:Ischemia Modified Albumin, IMA/AlbR:IMA Albumin ratio

In the assessment of the tests based on the cut-off values determined in the ROC analysis (accepting the result to be positive if results of both tests fell above the cut-off value, and negative if they fell below the cut-off value), they were found to be 87.5% and 88.9% for WBC-IMA (sensitivity; specificity), 80.9% and 84.2% for WBC-IMA/AlbR, 100% and 84.2% for NLR-IMA, 80.9% and 84.2% for NLR-IMA/AlbR, 71.4% and 96% for CRP-IMA, and 27.7% and 95.8% for CRP-IMA/AlbR.

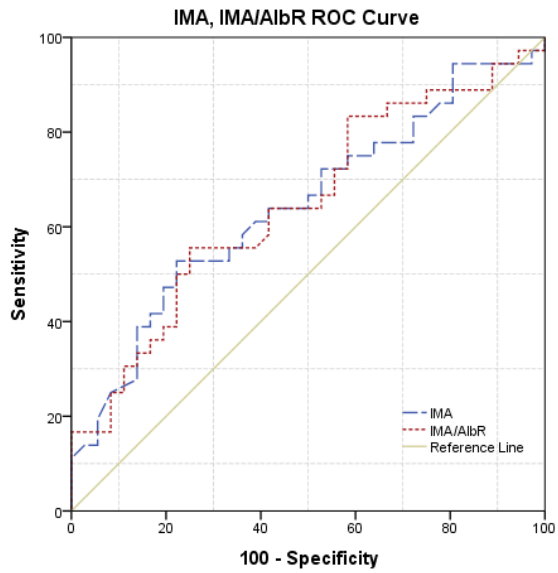

Figure 1: ROC curves for detection of appendicitis; IMA and IMA/AlbR parameters.

Table 2. ROC analysis results of the tests for the distinction of the Acute Appendicitis Group from the Non-Specific Abdominal Pain Group.

Tests parameters	Cut-Off	Sens	95% CI	Spec	95% CI	+LR	95%CI	-LR	95% CI	AUC	95% CI	*P*
WBC (1000/mm^3)#	>11.82	80.56	64.0 - 91.8	61.11	43.5 - 76.9	2.07	1.3 - 3.2	0.32	0.2 - 0.6	0.707	0.583 - 0.831	0.003*
NLR (%)#	>3.55	94.44	81.3 - 99.3	58.33	40.8 - 74.5	2.27	1.5 - 3.4	0.095	0.02 - 0.4	0.711	0.585 - 0.836	0.002*
CRP (mg/L)#	>20.7	50.00	32.9 - 67.1	86.11	70.5 - 95.3	3.60	1.5 - 8.6	0.58	0.4 - 0.8	0.709	0.589 - 0.829	0.002*
IMA (AbsU)#	>0.777	52.78	35.5 - 69.6	77.78	60.8 - 89.9	2.37	1.2 - 4.7	0.61	0.4 - 0.9	0.645	0.517 - 0.773	0.035*
IMA/AlbR (%)#	>16.71	55.56	38.1 - 72.1	75.00	57.8 - 87.9	2.22	1.2 - 4.2	0.59	0.4 - 0.9	0.647	0.519 - 0.775	0.032*

#:Values of the groups were calculated using the ROC curve. * :*P* values are statistically significant (*P*<0.05) ROC: Receiver Operating Characteristic, Sens: Sensitivity, Spec: Specificity, CI: Confidence Interval, LR: Likelihood Rate, AUC:Area under the curve, WBC: White blood cell, NLR: Neutrophile Lymphocyte Ratio, CRP: C-reactive protein, IMA: Ischemia Modified Albumin, IMA/AlbR:IMA Albumin ratio

The results of correlation analysis revealed that there was a weak correlation between age and CRP (r=-0.263, *P*=0.02) and correlations between WBC, NLR and the diameter of the appendix (respectively, r=0.637, *P*<0.001, r=0.497, *P*=0.007), between NLR and the diameter of the appendix (r=0.476, *P*=0.01), between CRP, albumin and IMA/AlbR (respectively, r=-0.460, *P*<0.001, and r=0.266, *P*=0.024), and between IMA/AlbR, IMA and albumin (respectively, r=0.943, *P*<0.001 and r=-0.468, *P*<0.001).

The results of the present study suggested that there were also significant increases in IMA and IMA/AlbR values in addition to WBC, CRP and NLR values, which were expected to be high in AA group.

DISCUSSION

Appendicitis is the most common disease requiring urgent surgery in pediatric patients and one of the most common reasons for hospital admissions, with 60,000-80,000 applications per year in pediatric age group in the USA. The prevalence of acute appendicitis is 7% in girls and 9% in boys. The life-time risk of appendectomy is 23.1% in women and 12% in men[13].

The frequency of acute appendicitis is associated with the development of lymphoid tissues and is mostly encountered in people aged between 10 and 30 years. The primary cause of AA is the obstruction of the blind-ended appendix lumen. When it is obstructed, fluid accumulates inside the appendix, thus resulting in distension and circulatory disorder, as well as bacterial invasion of the appendix wall. Late diagnosis causes perforation of the appendix and peritoneal spreading of the purulent material[14].

The diagnosis of AA in children is generally supported with laboratory and radiological examinations and established based on clinical findings. Although various diagnostic methods are used, it remains difficult to diagnose appendicitis, especially in children. Late diagnosis may lead to serious morbidity and even death. Thus, early and late diagnosis is of prime importance. However, no lab tests that show the early and late diagnosis for AA have come to the fore yet. Lab tests used to establish the diagnosis of AA in clinical practice generally include WBC and CRP tests. Yet, both tests have lower sensitivity and specificity. A stronger parameter is needed for the final diagnosis in suspicious cases[15-17].

In a meta-analysis study by Acharya *et al*, variables including WBC, CRP, bilirubin, procalcitonin, D-dimer and interleukin-6 for the diagnosis of AA were investigated. The sensitivity, specificity and AUC were found to be 79%, 55% and 0.75 for WBC and 76%, 50% and 0.80 for CRP, respectively. These variables were the most widely studied[18].

Yazici *et al* retrospectively examined 240 children who had undergone surgery due to AA and reported that 183 (76%) of these children were diagnosed with AA. WBC and NLR values were significantly higher in the AA group than the NSAP group. In the same study, they also found that sensitivity and specificity were 89% and 32% respectively for WBC (cut-off: 10.000), the sensitivity was 90% and 88% and specificity was 72% and 95%, respectively, for NLR >3.5 and NLR >5.0. They recommended using the cut-off value as 3.5 in the NLR test to establish differential diagnosis of abdominal pain and AA[15]. It was also found in the present study that the cut-off value for NLR was 3.55.

Sevinc *et al* examined the records of a total of 3,392 cases who had undergone an appendectomy based on a pre-diagnosis of AA by assigning the patients into three groups: normal appendix, acute appendix, and perforated appendix, based on their pathology results. The pathology results were compared with the commonly used primary lab tests. WBC, bilirubin and NLR were significant parameters for the diagnosis of AA. The cut-off values were 11.900/mm^3 for WBC (sensitivity: 71.2%; specificity: 67.2%; OR: 5.13), 1.0 mg/dl for bilirubin (sensitivity: 19.1%; specificity: 92.4%; OR: 2.96), and 3.0 for NLR (sensitivity: 81.2%; specificity: 53.1%; OR: 4.27)[19].

In their study, Ugur *et al* found that WBC, NLR and CRP values of AA group were significantly higher than those of abdominal pain group[17]. Additionally, in this study, WBC, NLR and CRP values of AA group were statistically significantly higher than the results of NSAP group. The results of the present study are

compatible with the literature. The results of ROC analysis conducted in the present study were found to be similar with previous studies in terms of WBC, NLR and CRP parameters, all of which are frequently used in the diagnosis of AA.

Stressful situations occurring at the cellular level as well as hypoxia, acidosis and free oxygen radicals lead to the deterioration of cell membrane functions. This medium causes the transformation of serum albumin into IMA. This transformation takes place within minutes after ischemia. IMA transforms back to normal albumin within 6 to 12 hours[20].

IMA level increases under ischemic and chronic conditions; however, it is not a tissue-specific marker. IMA is a marker that has been found to be associated especially with acute coronary syndrome. IMA level elevates in strangulated hernia, but returns to normal within 24 hours when the obstruction is removed[20-22]. IMA levels increase under some chronic ischemic conditions such as cancer, systemic sclerosis and end-stage renal failure. Some studies have revealed that the IMA increase is sensitive to diseases such as mesenteric ischemia, pulmonary embolism, stroke and ovarian torsion. In addition, IMA levels increase in many diseases with high oxidative stress such as obesity, type II diabetes mellitus, hypercholesterolemia, preeclampsia and polycystic ovarian syndrome[21,23-24].

In the study conducted by Nazik *et al* with AA (n=30) and healthy control groups (n=33), they found that the serum IMA levels were significantly higher in AA group (0.56±0.1) than healthy control group (0.33±0.1). In the same study, they obtained cut-off value of 0.445, sensitivity of 96.7, specificity of 99.7 and AUC of 0.991 for IMA in ROC analysis[25].

In addition, when comparing IMA and IMA/AlbR values of both groups, it was determined in the present study that IMA and IMA/AlbR values of AA group were statistically significantly higher than the values of NSAP group, which was an expected result.

ROC analysis in this study revealed that the cut-off value was 0.777 AbsU for IMA test (sensitivity: 52.78%, specificity: 77.78% and AUC: 0.645) and 16.71% for IMA/AlbR test (sensitivity: 55.56%, specificity: 75% and AUC: 0.647), in distinguishing the patients in AA group from those in NSAP group. The results of IMA in this study were relatively lower than the results found by Nazik *et al*[25]. In the present study, healthy control was not used and AA group and NSAP group were also compared with each other. This was the reason for the difference between them. In addition, the present study reflects the problem in emergency rooms even more.

When evaluating the tests based on the cut-off values determined in the ROC analysis (accepting the result to be positive if results of both tests fell above the cut-off value, and negative if they fell below the cut-off value), they were found to be 87.5/88.9 for WBC-IMA (sensitivity/specificity), 80.9/84.2 for WBC-IMA/AlbR, 100/84.2 for NLR-IMA, 80.9/84.2 for NLR-IMA/AlbR, 71.4/96 for CRP-IMA and 27.7/95.8 for CRP-IMA/AlbR.

When evaluating NLR and IMA together, 16 children had high NLR and IMA cut-off values, and all of them fell within the AA group. This result is very impressive and should be confirmed by future studies with more participants.

When examining the data of ROC analysis and comparing the AUC of the IMA and IMA/AlbR diagrams with the AUCs of WBC NLR, and CRP diagrams, it was determined that there was a very little difference between them, to the detriment of the IMA and IMA/AlbR. The specificity, sensitivity and accuracy rates of a test are of prime importance and these values are assessed according to the type of disease and its prevalence in the population. The test is required to have a high specificity rate unless advanced techniques are used to correct a misdiagnosis. If the test is used for screening purposes, then a high sensitivity rate is required. Tests with a high diagnostic value can reliably be used in diagnoses and screenings. In this study, IMA and IMA/AlbR tests had lower sensitivity values but higher specificity values compared to the other tests.

CONCLUSION

When IMA and IMA/AlbR were included into the classic tests, significant increases were observed in the sensitivity values, especially in the classic parameters' specificity values. This finding suggests that the parameters can be used together. Despite lower sensitivity values of IMA and IMA/AlbR, they could be added to the scoring and be used together with WBC, NLR and CRP tests for screenings. However, further studies with larger samples are needed.

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Authors' Contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Huseyin Kurku, Cuneyt Ugur, Hasan Madenci and Ozcan Erel. The first draft of the manuscript was written by Huseyin Kurku and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Ethical approval: The study plan was approved by the Ethics Committee of the Medical School, KTO Karatay University (Decision date: 10/01/2019, Decision no: 2019/004).

REFERENCES

1. Gans SL, Pols MA, Stoker J, Boermeester MA; expert steering group. Guideline for the diagnostic pathway in patients with acute abdominal pain. Dig Surg 2015; 32(1):23-31.
2. Tasar S, Tasar MA, Ayyildiz NK, Guder L, Arikan FI, Dallar YB. [Çocuk Acil Servisinde Akut Apandisit Tanısı İçin Pediatrik Apandisit Skorlamasının ve Ultrasonografi Bulgularının Değerleri.] Türkiye Çocuk Hastalıkları Dergisi 2015; 9(3):184-8. Article in Turkish.
3. Myers AL, Williams RF, Giles K, Waters TM, Eubanks 3rd JW, Hixson SD, *et al*. Hospital cost analysis of a prospective, randomized trial of early vs interval appendectomy for perforated appendicitis in children. J Am Coll Surg 2012; 214(4):427-35.
4. Breil T, Boettcher M, Hoffmann GF, Ries M. Publication status of completed registered studies in paediatric appendicitis: a cross-sectional analysis. BMJ Open 2018; 8(7):e021684.
5. Chan L, Shin LK, Pai RK, Jeffrey RB. Pathologic continuum of acute appendicitis: sonographic findings and clinical management implications. Ultrasound Q 2011; 27(2):71-9.
6. Burjonrappa S, Rachel D. Pediatric appendectomy: optimal surgical timing and risk assessment. Am Surg 2014; 80(5):496-9.
7. Sarac F, Sarsu SB, Yeniocak S, Sahin K, Yucetas E, Yildirim D, *et al*. The diagnostic value of irisin in pediatric patients with acute abdominal pain. Emerg Med Int 2018; 2018:3296536.
8. Palabiyik F, Kayhan A, Cimili T, Toksoy N, Bayramoglu S, Aksoy S. [The comparison of plain film and ultrasound findings of appendicitis in children.] Marmara Medical Journal 2008; 21:203-9. Article in Turkish.
9. Aksoy EK, Sapmaz F, Dogan O, Albuz O, Uzman M. Peptik ülserli hastalarda iskemi modifiye albumin düzeyleri. Akademik Gastroenteroloji Dergisi 2018; 17(2):74-7.
10. Das M, Cevik Y, Erel O, Corbacioglu SK. Ischemia-modified albumin levels in the prediction of acute critical neurological findings in carbon monoxide poisoning. The Kaohsiung Journal of Medical Sciences 2016; 32(4):201-6.
11. Yavuz F, Biyik M, Asil M, Dertli R, Demir A, Polat H, *et al*. Serum ischemic modified albumin (IMA) concentration and IMA/albumin ratio in patients with hepatitis B-related chronic liver diseases. Turk J Med Sci 2017; 47(3):947-53.
12. Bar–Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia—a preliminary report. J Emerg Med 2000; 19(4):311-5.
13. Howell EC, Dubina ED, Lee SL. Perforation risk in pediatric appendicitis: assessment and management. Pediatric Health Med Ther 2018; 9:135-45.
14. Koksal H, Uysal B, Saribabicci R. [Bir Devlet Hastanesinin Akut Apandisit Tecrübesi/Acute Appendicitis Experience of a State Hospital.] Journal of Academic Emergency Medicine 2010; 9(1):41-4. Article in Turkish.
15. Yazici M, Ozkisacik S, Oztan MO, Gursoy H. Neutrophil/lymphocyte ratio in the diagnosis of childhood appendicitis. Turk J Pediatr 2010; 52(4):400-3.
16. Ozyazici S, Karateke F, Turan U, Kuvvetli A, Kilavuz H, Karakaya B, *et al*. A novel oxidative stress mediator in acute appendicitis: thiol/disulphide homeostasis. Mediators of inflammation 2016; 2016:6761050.
17. Ugur C, Madenci H, Kurku H, Neselioglu S. The use of thiol/disulfide homeostasis parameters in the diagnosis of acute appendicitis in children. J Pediatr Infect Dis 2020; 15(4):195-9.
18. Acharya A, Markar SR, Ni M, Hanna GB. Biomarkers of acute appendicitis: systematic review and cost–benefit trade-off analysis. Surg Endosc 2017; 31(3):1022-31.
19. Sevinc MM, Kinaci E, Cakar E, Bayrak S, Ozakay A, Aren A, *et al*. Diagnostic value of basic laboratory parameters for simple and perforated acute appendicitis: an analysis of 3392 cases. Ulus Travma Acil Cerrahi Derg 2016; 22(2):155-62.
20. Gocmen AY, Erbay AR. [İskemi modifiye albümin miyokart perfüzyon sintigrafisi sonuçlarının ayırıcı tanısında faydalı olabilir mi?] Turk Kardiyol Dern Ars 2016; 44(5):380-8. Article in Turkish.
21. Nazik H, Nazik S, Kusku-Kiraz Z, Gul FC. Evaluation of ischemia-modified albumin level and parameters related with oxidative stress in early onset androgenetic alopecia. Deri Hastaliklari ve Frengi Arsivi 2017; 51(4):115-8.
22. Kadioglu H, Omur D, Bozkurt S, Ferlengez E, Memmi N, Ersoy YE, *et al*. Ischemia modified albumin can predict necrosis at incarcerated hernias. Dis Markers 2013; 35(6):807-10.
23. Yildirim A, Yildirim S, Topaloglu N, Tekin M, Kucuk A, Erdem H, *et al*. Correlation of ischemia-modified albumin levels and histopathologic findings in experimental ovarian torsion. Turk J Emerg Med 2016; 16(1):8-11.
24. Gunduz A, Turkmen S, Turedi S, Mentese A, Yulug E, Hulya Ulusoy, *et al*. Time-dependent variations in ischemia-modified albumin levels in mesenteric ischemia. Acad Emerg Med 2009; 16(6):539-43.
25. Nazik S, Avci V, Kusku Kiraz Z. Ischemia-modified albumin and other inflammatory markers in the diagnosis of appendicitis in children. Turk J Trauma Emerg Surg 2017; 23(4):317-21.

Original Article

The relationship between the collapsibility index of the internal jugular vein and spinal anesthesia-induced hypotension in Cesarean section

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ABSTRACT

Objective: We aimed to investigate the sonographic assessments of internal jugular vein (IJV) to predict spinal anesthesia induced-hypotension in pregnant patients undergoing a cesarean section.
Design: A prospective, observational study
Setting: Bursa Yuksek Ihtisas Training and Research Hospital
Subjects: Seventy-nine American Society of Anesthesiologists physical status II, healthy pregnant women at term aged over 18 years who were scheduled for an elective cesarean section with spinal anesthesia were included in the study.
Intervention: Sonographic assessment of the IJV was made in the supine position with an estimated 15° left lateral table tilt before spinal anesthesia. Spinal anesthesia was performed for all patients. We administered 20 mL/kg crystalloid to patients as co-loading. Collapsibility index (CI) [(dIIJVmax-dIJVmin)/dIJVmax × 100%], aspect ratio (height/width), and the maximum diameter of the IJV (dIJVmax) were measured preoperatively. The upper sensory level was assessed. Hypotension was defined as a more than 20% decrease in systolic blood pressure from the baseline level.
Main outcome measure: The relationship between spinal anesthesia-induced hypotension and dIJVmax, IJV-CI and IJV aspect ratio.
Results: Seventy-three patients were analyzed. The incidence of hypotension was 60.3% (n=44). There were no significant differences in IJV-CI (50±1.6, 51±2), IJV aspect ratio (1.02±0.30, 1.11±0.50) and dIJVmax (1.00±0.36, 1.03±0.26) between developed hypotension group and undeveloped hypotension group. The upper sensory level was also not significantly different between the groups.
Conclusion: We found that dIJVmax, IJV aspect ratio and IJV-CI were not predictive of spinal anesthesia-induced hypotension for cesarean section.

KEY WORDS: collapsibility index, hypotension, internal jugular vein, spinal anesthesia, ultrasound

INTRODUCTION

Hypotension is the most common complication of spinal anesthesia. If no precautions are taken, hypotension develops in 80-90% of patients[1,2]. Maternal symptoms such as nausea, vomiting, dyspnea, cardiac arrest and collapse frequently accompany severe hypotension, and adverse effects on the fetus, including depressed Apgar scores, neonatal acidosis and neurologic deficit have been correlated with the severity and duration of hypotension[1-3]. A patients susceptibility to intraoperative hypotension is influenced by a surgical patient's preoperative volume status that may change due to comorbidities, and preoperative treatments such as bowel preparation and fasting[4,5]. Knowing intravascular volume status is important for physicians. Measurement of central venous pressure (CVP), a traditional method, is invasive and often inaccurate[6]. In many clinical cases such as tricuspid regurgitation, heart failure and right heart failure, hypovolemia and hypervolemia

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show pressure, and volume change within the intrathoracic systemic venous compartment. A change due to hypovolemia or hypervolemia also reflects in extrathoracic veins, primarily in the intraabdominal inferior vena cava (IVC) or extrathoracic internal jugular vein (IJV)[7,8].

Recently, it has been shown that sonographic determination of the diameter of the IVC and IJV is related to CVP and other hemodynamic parameters describing the patient's volume status[9,10]. IVC measurements are not possible in 10-15% of patients because of morbid obesity, pregnancy or excessive bowel gas[11,12]. IJV imaging is easier to perform than IVC visualization in pregnant patients and does not require transthoracic echocardiography. The present study investigated the use of IJV to predict spinal anesthesia-induced hypotension in pregnant patients undergoing a cesarean section.

SUBJECTS AND METHODS

Ethics approval

This was a prospective, observational and single-center study of pregnant patients conducted between October 2017 and February 2018. The study protocol was approved by the Local Ethics Committee and the protocol for this clinical trial was registered at the Australian New Zealand Clinical Trials (ACTRN12618001067268). The study was conducted following the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient.

Patients

Seventy-nine term pregnant women aged over 18 years, who were American Society of Anesthesiologists status II, and undergoing elective cesarean section with spinal anesthesia were included in the study. The patients with gestational age less than 37 weeks, chronic hypertension, multi-fetus pregnancy, preeclampsia, gestational diabetes, pre-pregnancy obesity, history of pregnancy-related complications and severe medical conditions such as pulmonary, liver and kidney disease were excluded from the study. Patients with a baseline systolic blood pressure (SBP) higher than 150 mm Hg and mean blood pressure (MBP) lower than 70 mm Hg were also excluded.

IJV ultrasonography (USG)

All measurements were performed in the operating room. Blood pressure and heart rate were measured in the supine position with an estimated 15° left lateral table tilt to minimize aortocaval compression by the uterus. After a stabilization interval of 3-5 minutes, baseline blood pressure measurements were made at least three times and averages were recorded. We used the non-invasive oscillometric method with an appropriately sized cuff. The anteroposterior IJV diameter was measured using M-mode during a respiratory cycle in the supine position with an estimated 15° left lateral table tilt. The USG examination was performed with a 15-MHz linear transducer probe (Esaote®MyLab 30, Florance, Italy). Right IJV measurements were obtained at the level of the cricoid cartilage using the method described by Keller *et al*[13]. USG probe was used to avoid changes in vein diameter unrelated to respiratory variation and to collapse IJV and distinguish it from the carotid artery, gentle pressure by the ultrasonography probe was used. Then the pressure was relieved to the USG probe-skin interface. For true measurement, attention was given to avoid the influence of probe compression on IJV dimensions during the USG examination, and in order to avoid the interference of probe to-vein angle, the IJV evaluation was performed by positioning the probe perpendicular to the skin and oriented orthogonally to the IJV short-axis diameter[14]. USG measurements including the maximum diameter of the IJV (dIJVmax) at the end of expiration during spontaneous respiration, collapsibility index (CI) and aspect ratio were recorded. The IJV CI (%) was calculated as [(dIJVmax - dIJVmin)/ dIJVmax] x 100%[15]. IJV aspect ratio was defined as its height (anterior-posterior diameter) divided by its width[13]. All of the USG images were made by the primary investigator, who had similarly performed >30 cases before starting the study.

Anesthesia management

Single-shot spinal anesthesia was then performed in the sitting position at L_{3-4} or L_{4-5} using a 25-G Quincke needle. A dose of either 10 mg (height <160 cm) or 12 mg (height ≥160 cm) of 0.5% hyperbaric bupivacaine was injected over 30 seconds with the orifice-directed cephalad. Immediately after the injection, the patient was returned to the supine tilted position, and blood pressure and heart rate measurements were taken. We administered 20 mL/kg crystalloid (Ringer lactate®, Polifarma, Istanbul, Turkey) to patients as co-loading. The sensory level was assessed using the pinprick test. Surgery was started after attaining an upper sensory level of T_6 or higher. Hypotension was defined by a more than 20% decrease in SBP from the baseline level. The SBP and MBP reading before IJV USG were defined as a baseline. SBP was recorded every three minutes throughout the study period and ephedrine 5 and 10 mg boluses were administered when the SBP decreased below 80% (hypotension), and 70% (severe hypotension) of the baseline value, respectively. The patients were divided into two groups as those who developed hypotension and developed no hypotension.

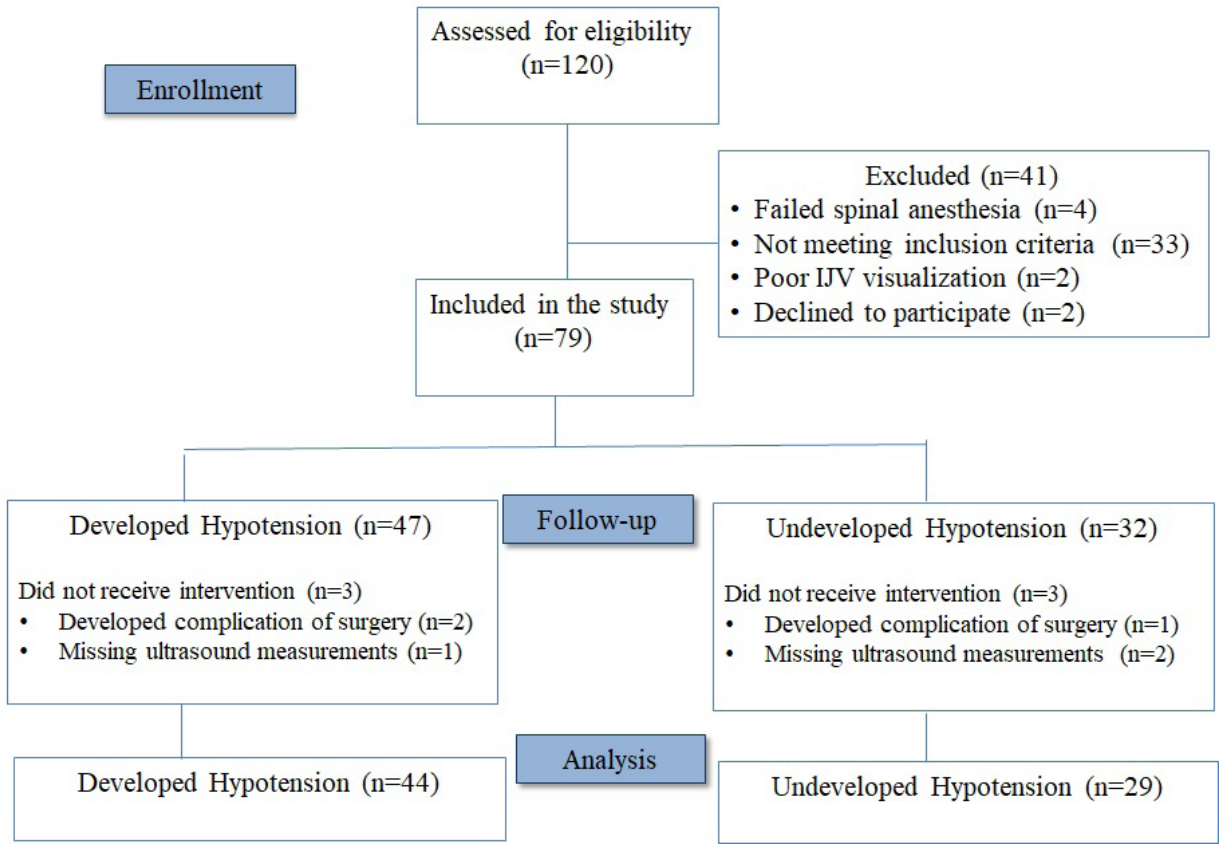

Figure 1: Flow chart of the study

Outcomes

The primary outcome was the relationship between spinal anesthesia-induced hypotension and dIJVmax, IJV-CI and IJV aspect ratio. The secondary outcomes were the number of patients requiring ephedrine and upper sensory level.

Statistical analysis

A pilot study of 15 patients detected a decrease in SBP. The analysis indicated a sample size of 73 patients was needed to provide 80% power and a 5% level of significance to detect a 33% effect size. The Shapiro-Wilk test was used as a normality test. Continuous variables were compared using Student's t-test, and the Mann-Whitney U test was used when the data were not normally distributed. Categorical variables were compared using Pearson's Chi-square test and Fisher's exact test. Paired data were analyzed using the paired t-test, and the Wilcoxon signed-rank test was used when data were not normally distributed. For responses at different time points, percent changes were calculated according to baseline measurements. These percent changes were compared using the Mann-Whitney U test for two groups and the Kruskal-Wallis test for more than two groups. Correlations between variables were tested using Pearson and Spearman correlation coefficients. A *P*-value <0.05 was considered significant. All statistical analyses were performed using the IBM SPSS ver. 23.0 software package.

Table 1: Comparison of patients characteristics between patients who developed and did not develop hypotension after spinal anesthesia

Variables	Developed hypotension		*P*
	Yes (n=44)	No (n=29)	
Age, years	30.66±5.39	30.38±4.13	0.813
Height, cm	160.23±5.46	162.24±4.80	0.111
Weight, kg	78.73±13.65	79.90±12.35	0.711
dIJVmax, cm	1.00±0.36	1.03±0.26	0.741
Collapsibility index, %	50±1.6	51±2	0.764
Aspect ratio	1.02±0.30	1.11±0.50	0.373
Upper sensory level	T4 (2-6)	T5 (3-6)	0.061
The amount of crystalloid consumption intraoperatively, ml	1734.78±360.13	1690.90±367.05	0.251
Baseline SBP, mmHg	136.04±13.27	133.14±13.55	0.367
Baseline MBP, mmHg	97.16±12.24	93.41±11.17	0.190
Baseline HR, beats/min	96.90±15.65	90.34±14.83	0.078
SBP % decrease	-0.18±0.12	-0.12±0.09	0.016

dIJVmax: maximum diameter of the internal jugular vein; SBP: systolic blood pressure; MBP: mean blood pressure; HR: heart rate

Table 2: Logistic regression analysis results of patients for hypotension after spinal anesthesia

Variables				95% CI for OR	
	B	*P*	OR	Lower	Upper
Age, years	0.050	0.415	1.051	0.932	1.186
Height, cm	-0.059	0.309	0.942	0.841	1.057
Weight, kg	-0.015	0.525	0.985	0.939	1.032
Gestational age (week)	-0.381	0.325	0.683	0.320	1.460
Upper sensory level	-0.632	0.085	0.532	0.259	1.091
dIJVmax (cm)	-0.362	0.719	0.696	0.097	5.001
Collapsibility index	-1.110	0.511	0.330	0.012	9.016
Aspect ratio	-0.425	0.586	0.654	0.142	3.013
Baseline SBP	0.001	0.978	1.001	0.942	1.063
Baseline MBP	0.034	0.338	1.035	0.965	1.111

CI: confidence ınterval; OR: odds ratio; dIJVmax: maximum diameter of the internal jugular vein; SBP: systolic blood pressure; MBP: mean blood pressure

RESULTS

One hundred and twenty patients were screened in the study and 47 patients were excluded. Data from the remaining 73 patients were analyzed. Full details of patients included in the study are shown in the flow chart of the study in Figure 1.

The characteristics of patients are summarized in Table 1. After spinal anesthesia, hypotension developed in 44 (60.3%) patients according to the study criteria. Thirty-seven (50.68%) patients received ephedrine (14.32±7.67 mg) for severe hypotension lasting more than 2 minutes. When the patient's heart rate was below 50, one patient received atropine for bradycardia. The upper sensory level was not significantly different between the groups (Table 1, *P*>0.05). There were no significant differences in IJV-CI, IJV aspect ratio and dIJVmax between the groups (Table 1). Receiver operating characteristics curve analysis for predicting hypotension was not calculated because there were no significant differences in measurements.

The logistic regression analysis for spinal anesthesia-induced hypotension is shown in Table 2. We did not find significant independent predictive factors of hypotension. There were no significant correlations in SBP 20% decrease with IJV-CI, IJV aspect ratio and dIJVmax (Figure 2).

DISCUSSION

Determining the initial volume status of patients and administering a prophylactic vasopressor is important to prevent hypotension in patients who are undergoing cesarean section with spinal anesthesia. Sonographic measurement of the diameter of the IJV or IVC is related to CVP and other hemodynamic parameters describing the patient's volume status, and is important to anesthesiologists in an opportunity to predict hypotension. We investigated whether preoperative USG measurements of IJV could predict spinal anesthesia-induced hypotension in pregnant patients undergoing a cesarean section. In the current study, hypotension was developed in 44 patients (60.3%). We found that dIJVmax, IJV aspect ratio and IJV-CI were not predictive of spinal anesthesia-induced hypotension.

There are different definitions for hypotension[3]. We chose the definition as a more than 20% decrease in SBP from the baseline level like Tawfik *et al*'s[16] study. Applying these different definitions to a cohort of women having an elective cesarean section with neuraxial blocks gave incidences for hypotension varying between 7.4% and 74.1%[3]. In our study, the incidence of spinal anesthesia-induced hypotension was 60.3% in cesarean section, similar to the literature.

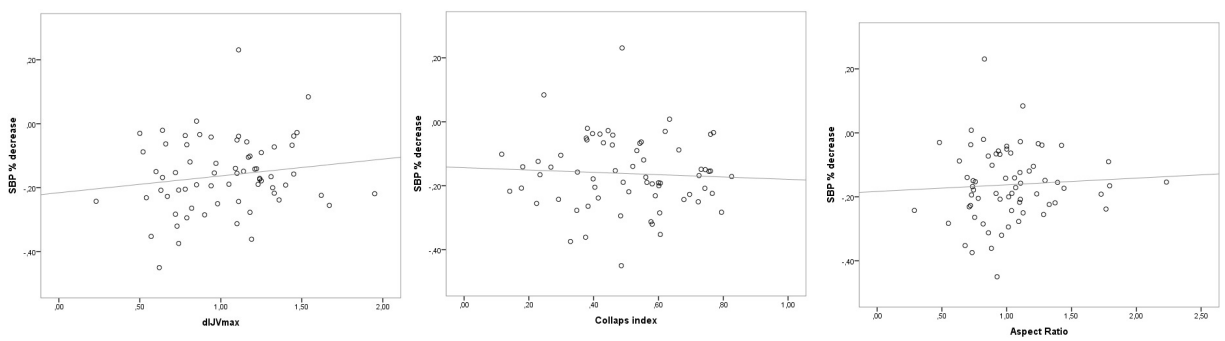

Figure 2: Correlation in SBP 20% decrease with IJV-CI, IJV aspect ratio and dIJVmax

Although sonographic assessment of the IVC has been investigated in anesthesia and intensive care unit to evaluate the volume status and predict fluid responsiveness, there are only a few studies about pregnant women[16,17]. Comparison of literature about the anesthesia-induced hypotension and sonographic parameters of the IVC or IJV were summarized in Table 3. To our knowledge, no studies have investigated the relationship between IJV-CI and spinal anesthesia-induced hypotension on pregnant women.

Hernandez *et al*[18] researched the IVC diameter in response to 1 L of intravenous hydration in term pregnancy with epidural analgesia for normal vaginal delivery. They found that hydration was not accompanied by any significant change in heart rate, MBP or IVC-CI. With the initiation of epidural anesthesia, the MBP decreased significantly from 88 to 80 mm Hg, but the heart rate and IVC-CI remained unchanged. In their study[18], there was no difference in IVC-CI. However, the rate of hypotension is lower in epidural analgesia compared with spinal analgesia. MBP values are higher than 60 mm Hg in both their groups. They reported that the IVC diameter might prove useful in obstetric states in which rapid confirmation of intravascular volume changes is important for guiding therapy, such as obstetric hemorrhage, management of dialysis in chronic kidney disease, severe cardiac disease and oliguria from various causes[18].

Zhang *et al*[5] demonstrated that preoperative USG measurement of the IVC-CI was a reliable predictor of hypotension after induction of general anesthesia. In our study, preoperative ultrasound measurements of dIJVmax, aspect ratio and IJV-CI were not a predictor of spinal anesthesia-induced hypotension for cesarean section.

Ceruti *et al*[17] evaluated IVC USG-guided volume optimization to prevent postspinal hypotension in non-obstetric surgery. The authors found that the IVC-CI was correlated with the amount of fluid administered (R^2=0.32), but could not be used to predict spinal anesthesia-induced hypotension. We performed IJV imaging in obstetric patients without using volume management according to USG, unlike Ceruti *et al*'s[17] study, and we found no significant relationship between IJV-CI and hypotension.

Tawfik *et al*[16] searched maternal hemodynamics using a combination of 500 mL crystalloid co-load and 500 mL colloid preload versus 1000 mL crystalloid co-load. They assessed the IVC at baseline and at the following time points after spinal anesthesia. Their specific administered fluid strategies don't significantly influence the incidence and severity of hypotension. When hypotension develops in spite of fluid administration, vasopressors are still required[16]. The degree of systemic vascular resistance is also an important role of spinal anesthesia-induced hypotension as well as preoperative volume status. We think that further studies are needed to investigate the degree of systemic vascular resistance.

Of the possible strategies for fluid administration during spinal anesthesia in cesarean delivery, crystalloid preload has been demonstrated to have minimal or no effect in reducing the incidence and

Table 3: Comparison of literature about the anesthesia induced hypotension and sonographic measurements of the IVC or IJV

Authors	n	Anesthesia Technique	Patients	Research Parameters	Comments
Zhang *et al*[5]	90	General anesthesia	Non-obstetric	IVC Diameter, Collapsibility	IVC-CI was a reliable predictor of hypotension after induction of general anesthesia
Ceruti *et al*[17]	160	Spinal anesthesia	Non-obstetric	IVC Collapsibility	The IVC-CI was correlated with the amount of fluid administered IVC-CI could not be used to predict postspinal anesthesia hypotension
Tawfik *et al*[16]	198	Spinal anesthesia	Obstetric	IVC Collapsibility	The IVC can be reliably viewed in the long axis using the subcostal window in parturients before and during cesarean delivery The maximum and minimum IVC diameters and the IVC-CI can be used to assess the volume status
Kuwata *et al*[20]	50	Spinal anesthesia	Obstetric	Pleth variability index, Perfusion index	Pleth variability index after spinal anaesthesia was a good predictor of spinal anaesthesia-induced hypotension Perfusion index change after spinal anaesthesia has the potential to predict hypotension.
Hernandez *et al*[18]	24	Epidural analgesia	Obstetric	IVC Diameter Collapsibility	They found that hydration was not accompanied by any significant change in CI.
Current study	73	Spinal anesthesia	Obstetric	IJV Diameter Collapsibility Aspect ratio	dIJVmax, IJV aspect ratio, and IJV-CI were not predictive of hypotension induced spinal anesthesia

IVC: Inferior vena cava; IJV: internal jugular vein; CI: Collapsibility index; dIJVmax: maximum diameter of the internal jugular vein

severity of hypotension, and the other strategies (colloid preload and crystalloid or colloid co-load) seem to be comparably effective[19]. We used 20 mL/kg crystalloid co-load and no preloading for our patients. Future clinical research should focus on the effectiveness of preloading before spinal anesthesia and the relationship between CI and hypotension.

Keller *et al*[13] suggested that the IJV aspect ratio can be useful for identifying patients with a low CVP in spontaneously breathing patients. They found that IJV aspect ratio <0.75 in predicting a CVP <10 mm Hg[13]. The IJV aspect ratio was assessed easily and was found to be over 0.75 in our two groups. If compared to the study of Keller *et al*[13], all patients' CVP could be accepted over 10, because the IJV aspect ratio was found to be over 0.75 in our study. We did not include patients who had pathologic volume depletion or excess and therefore did not assess the assessment of IJV in these situations.

Kuwata *et al*[20] investigated the efficacy of pleth variability index and perfusion index to estimate maternal volume status. They demonstrated that PVI and PI change after spinal anesthesia were good predictors of spinal anesthesia-induced hypotension in patients undergoing a cesarean section. According to the literature, only 34% of anesthesiologists in America and Europe used cardiac output monitoring in high-risk surgery[21]. For this reason, many anesthesiologists use a very simple hemodynamic monitoring level (for example, blood pressure, heart rate), and therefore the inclusion of the ultrasonographic assessment of IVC or IJV helps to identify patients who need fluid optimization. We have no cardiac output monitoring in our study.

Bauman *et al*[22] demonstrated that IVC-CI and IJV-CI were correlated in the setting of spontaneous breathing. However, IVC-CI and IJV-CI were not correlated during increased thoracic pressure or increased intraabdominal pressure. Our measurements were made in spontaneous breathing. Kent *et al*[23] verified positive correlations between IJV-CI versus IVC-CI (R^2=0.38). We preferred to use IJV in pregnant patients because of the easier imaging than IVC.

Our study has some limitations. Our primary limitations were not using invasive blood pressure measurement, and we did not include invasive hemodynamic parameters such as pleth variability index, perfusion index, cardiac output and CVP. We did not evaluate the change in IJV diameters after spinal anesthesia, crystalloid co-load, and at the time developed hypotension. We cannot generalize our results because of the different definitions of hypotension; our results might change depending on the definitions used. The other limitation is the lack of synchronous evaluation of IVC.

CONCLUSION

We found that dIJVmax, IJV aspect ratio and IJV-CI were not predictive of spinal anesthesia-induced hypotension in cesarean section. IJV-CI could be an alternative option to when access to IVC-CI is unavailable, because it is relatively easier and faster to obtain than IVC-CI measurements in term pregnant patients. Future research is needed to determine the relationship between IJV measurements and spinal anesthesia-induced hypotension in obstetric patients with invasive hemodynamic parameters.

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Author contribution: Derya Karasu, Cagdas Baytar, Canan Yilmaz and Seyda Efsun Ozgunay performed study design, literature review and article writing; Guven Ozkaya did the analysis and article writing.
Conflict of interest: None

REFERENCES

1. Kinsella SM, Carvalho B, Dyer RA, Fernando R, McDonnell N, Mercier FJ, *et al.* International consensus statement on the management of hypotension with vasopressors during caesarean section under spinal anaesthesia. Anaesthesia 2018; 73(1):71-92.
2. Tsen LC. Anesthesia for Cesarean Delivery. In: Chestnut DH, Wong CA, Tsen LC, Ngan Kee W, Beilin Y, Mhyre J, editors. Chestnut's Obstetric Anesthesia Principles and Practice. 5th ed. Phidelphia: Elseiver Saunders; 2014. p 545-603.
3. Klohr S, Roth R, Hofmann T, Rossaint R, Heesen M. Definitions of hypotension after spinal anaesthesia for caesarean section: literature search and application to parturients. Acta Anaesthesiol Scand 2010; 54(8):909-21.
4. Charlson ME, MacKenzie CR, Gold JP, Ales KL, Topkins M, Shires GT. Preoperative characteristics predicting intraoperative hypotension and hypertension among hypertensives and diabetics undergoing noncardiac surgery. Ann Surg 1990; 212(1):66-81.
5. Zhang J, Critchley LAH. Inferior vena cava ultrasonography before general anesthesia can predict hypotension after induction. Anesthesiology 2016; 124(3):580-589.
6. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? a systematic review of the literature and the tale of seven mares. Chest 2008; 134(1):172-8.
7. Guarracino F, Baldassarre F, Forfori F, Bertini P, Magliacano L, Pinsky MR. Jugular vein distensibility predicts fluid responsiveness in septic patients. Crit Care 2014; 18(6):647.
8. Chiaco JMC, Parikh NI, Fergusson DJ. The jugular venous pressure revisited. Cleve Clin J Med 2013; 80(10):638-44.
9. Thudium M, Klaschik S, Ellerkmann RK, Putensen C, Hilbert T. Is internal jugular vein extensibility associated with indices of fluid responsiveness in ventilated patients? Acta Anaesthesiol Scand 2016; 60(6):723-33.

10. Pellicori P, Kallvikbacka-Bennett A, Zhang J, Khaleva O, Warden J, Clark AL, *et al*. Revisiting a classical clinical sign: jugular venous ultrasound. Int J Cardiol 2014; 170(3):364-70.
11. Broilo F, Meregalli S, Friedman G. Right internal jugular vein distensibility appears to be a surrogate marker for inferior vena cava vein distensibility for evaluating fluid responsiveness. Rev Bras Ter Intensiva 2015; 27(3):205-11.
12. Nagdev AD, Merchant RC, Tirado-Gonzalez A, Sisson CA, Murphy MC. Emergency department bedside ultrasonographic measurement of the caval index for noninvasive determination of low central venous pressure. Ann Emerg Med 2010; 55(3):290-5.
13. Keller AS, Melamed R, Malinchoc M, John R, Tierney DM, Gajic O. Diagnostic accuracy of a simple ultrasound measurement to estimate central venous pressure in spontaneously breathing critically ill patients. J Hosp Med 2009; 4(6):350-5.
14. Prekker ME, Scott NL, Hart D, Sprenkle MD, Leatherman JW. Point-of-care ultrasound to estimate central venous pressure: a comparison of three techniques. Crit Care Med 2013; 41(3):833-41.
15. Kent A, Bahner DP, Boulger CT, Eiferman DS, Adkins EJ, Evans DC, *et al*. Sonographic evaluation of intravascular volume status in the surgical intensive care unit: a prospective comparison of subclavian vein and inferior vena cava collapsibility index. J Surg Res 2013; 184(1):561-6.
16. Tawfik MM, Tarbay AI, Elaidy AM, Awad KA, Ezz HM, Tolba MA. Combined colloid preload and crystalloid coload versus crystalloid coload during spinal anesthesia for cesarean delivery: a randomized controlled trial. Anesth Analg 2019; 128(2):304-12.
17. Ceruti S, Anselmi L, Minotti B, Franceschini D, Aguirre J, Borgeat A, *et al*. Prevention of arterial hypotension after spinal anaesthesia using vena cava ultrasound to guide fluid management. Br J Anaesth 2018; 120(1):101-8.
18. Hernandez CA, Reed KL, Juneman EB, Cohen WR. Changes in sonographically measured inferior vena caval diameter in response to fluid loading in term pregnancy. J Ultrasound Med 2016; 35(2):389-94.
19. Melchor JR, Espinosa Á, Hurtado EM, Francés RC, Pérez RN, Gurumeta AA, *et al*. Colloids versus crystalloids in the prevention of hypotension ınduced by spinal anesthesia in elective cesarean section. a systematic review and meta-analysis. Minerva Anestesiol 2015; 81(9):1019-30.
20. Kuwata S, Suehiro K, Juri T, Tsujimoto S, Mukai A, Tanaka K, *et al*. Pleth variability index can predict spinal anaesthesia-ınduced hypotension in patients undergoing caesarean delivery. Acta Anaesthesiol Scand 2018; 62(1):75-84.
21. Cannesson M, Pestel G, Ricks C, Hoeft A, Perel A. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. Crit Care 2011; 15(4):R197.
22. Bauman Z, Coba V, Gassner M, Amponsah D, Gallien J, Blyden D, *et al*. Inferior vena cava collapsibility loses correlation with internal jugular vein collapsibility during increased thoracic or intra-abdominal pressure. J Ultrasound 2015; 18(4):343-8.
23. Kent A, Patil P, Davila V, Bailey JK, Jones C, Evans DC, *et al*. Sonographic evaluation of intravascular volume status: can internal jugular or femoral vein collapsibility be used in the absence of IVC visualization? Ann Thorac Med 2015; 10(1):44-9.

Original Article

Current status of interventional radiology practice in Saudi Arabia

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ABSTRACT

Objective: To study the current status of interventional radiology (IR) practice in Saudi Arabia
Design: Cross-sectional study
Setting: Multiple hospitals of different healthcare sectors in Saudi Arabia
Subjects: Interventional radiologists in Saudi Arabia
Intervention: A cross-sectional survey targeting interventional radiologists in Saudi Arabia was conducted using an electronic questionnaire.
Main outcome measures: The questions aimed to gather information about the demographics of interventional radiologists, clinical and technical aspects of IR practice, and challenges facing this specialty.
Results: The response rate was 56% (54 respondents out of 97 interventional radiologists). Ninety-six percent of respondents were males, and 4% were females. Eighty percent were consultants, 41% were trained in North America, 22% in Saudi Arabia, and 19% in Europe. Fifty-two percent of respondents ran independent IR clinics, 81% did not have admission privileges, 54% did not do clinical rounds and 80% did not have protected research time. Several challenges and obstacles were reported, including financial limitations (26%), competition and lack of cooperation from other specialties (24%), lack of patients and public awareness (17%), lack of administrative support (11%) and shortage of IR doctors and staff (11%).
Conclusion: The results of this survey provided background information about IR in Saudi Arabia. Variations in IR practice among interventional radiologists, in addition to several challenges and obstacles, were reported. Establishment of national practice guidelines and collaboration among multiple concerned parties to overcome the challenges are recommended.

KEY WORDS: interventional radiology, practice, Saudi Arabia

INTRODUCTION

Interventional radiology (IR) is a relatively young specialty compared to most other medical and surgical specialties. It is expanding rapidly worldwide and is becoming a cornerstone in providing medical care to a diverse group of patients in many hospitals. A wide spectrum of vascular and non-vascular interventional procedures are performed daily by interventional radiologists with a great valuation of this service by other specialties[1].

Saudi Arabia has a population of more than 31 million, with one of the top 20 economies in the world[2]. The healthcare system in Saudi Arabia is constituted of several sectors, including the ministry of health (MOH), university hospitals, private hospitals, National Guard health affairs, Ministry of Defense hospitals, Ministry of Interior hospitals and King Faisal specialist hospitals.

There are approximately one-hundred interventional radiologists practicing in several hospitals of different healthcare sectors in Saudi Arabia. Different training backgrounds of the interventional radiologists and lack of unified national practice guidelines may lead to variations in Saudi Arabia. Various challenges and obstacles, including lack of information related to its practice, face this specialty.

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This study aimed to provide a reference point for and background information about the current status of IR practice in Saudi Arabia. A literature search was conducted and did not reveal any other studies that covered this topic previously.

SUBJECTS AND METHODS

This was a cross-sectional study that targeted interventional radiologists who practice in Saudi Arabia. The regional research ethics committee approved this study. An anonymous electronic survey consisting of 23 questions (appendix) was created on Google Forms (Google LLC, Mountain View, CA, USA). The participation link was sent electronically to the members of the Saudi Interventional Radiology Society, who had 102 members at the time of the survey. The questionnaire was open for participation for a period of one month, from October 30 to November 30, 2017, with three reminders sent during that period. Statistical analysis was done by calculating the percentage of different responses to each question with multivariate analysis to link responses of different questions.

RESULTS

Demographic results

The link of the survey reached 97 interventional radiologists who were eligible to participate. Out of them, 54 responses were received. Therefore, the response rate was 55.7%. Approximately, 80% (43/54) of the respondents were consultants, 13% (7/54) specialists, 7% (4/54) fellows, 96% (52/54) males, and only 4% (2/54) were females. The experience of 44% (24/54) of the respondents was less than 5 years, while 24% (13/54) had more than 10 years of experience, and 32% (17/54) had 5 to 10 years of experience. The highest number of respondents (22/54, 41%) were trained in North America, followed by Saudi Arabia (12/54, 22%) and Europe (10/54, 19%). The rest of the respondents completed their training in various other countries. The majority of the respondents (85%, 46/54) were vascular and interventional radiologists, followed by neuro-interventional radiologists (7%, 4/54), pediatric (4%, 2/54), and non-vascular ones (4%, 2/54). The MOH was the sector with the highest number of interventional radiologists (27/54, 50%) followed by the National Guard for health affairs (11/54, 20%), as shown in Figure 1. Ninety-eight percent (53/54) of the respondents reported holding valid basic life support certificates, 37% (20/54) are certified for advanced life support, and 65% (35/54) carry conscious sedation certificates.

Clinical practice results

The majority of the respondents reported running an independent IR clinic (52%, 28/54; out of them, 54% (15/28) work in the MOH), not having admission privileges (81%, 44/54), not doing clinical rounds (54%, 29/54), not being trainers or trainees in IR fellowship programs (59%, 32/54), having no protected research time (80%, 43/54), practicing diagnostic radiology besides IR (56%, 30/54), and obtaining informed consent for minor procedures (78%, 42/54). Protected research time is granted to all respondents in university hospitals, 50% in King Faisal specialist hospitals, 40% in the Ministry of Defense hospitals, 20% in the National Guard hospitals, and to only 4% in the MOH hospitals.

Eighty-two percent of the respondents (44/54) reported performing trans-arterial chemoembolization procedures, 76% (41/54) perform radiofrequency ablation, 46% (25/54) perform trans-arterial radioembolization, 44% (24/54) perform microwave ablation, 4% (2/54) perform cryoablation, 2% (1/54)

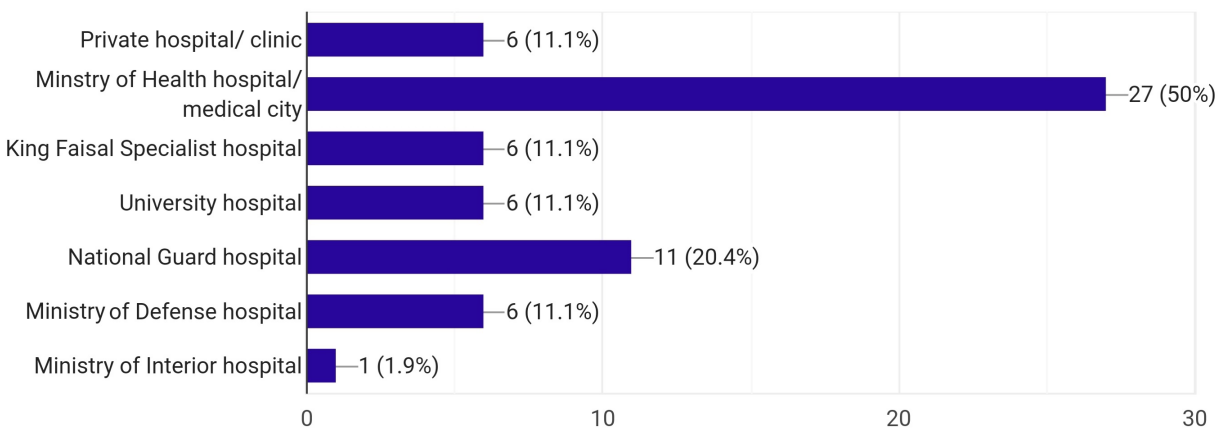


Fig 1: Distribution of respondents by sector of practice. Note: Some respondents work in more than one sector, which is why the total number/percentage exceeded 54/100%.

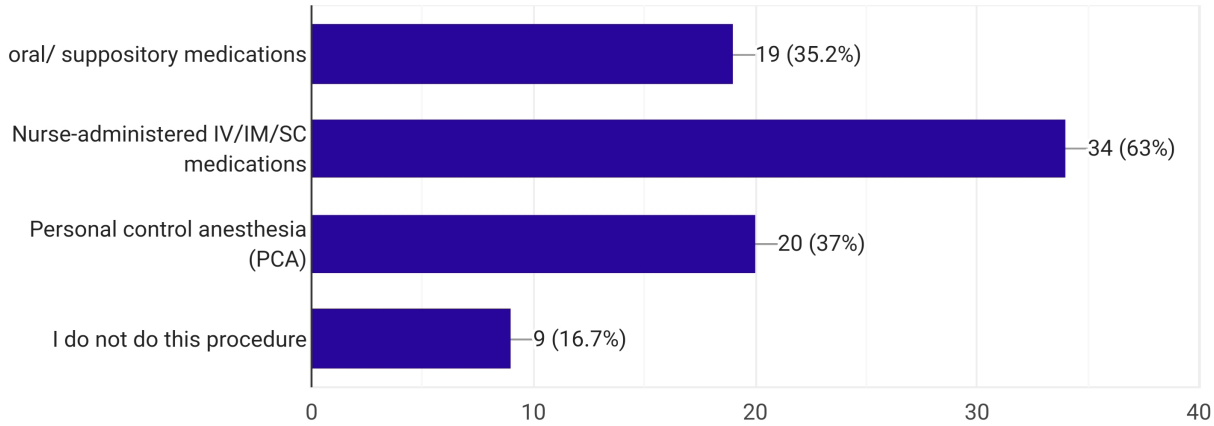


Fig 2: Responses regarding pain control medication during the post-procedure hospital stay for uterine fibroid embolization (UFE).

perform irreversible electroporation and 19% (10/54) reported not performing any of these interventional oncology procedures.

The most frequently performed procedures are venous and dialysis procedures (46% of the respondents; 44% of them work in MOH), percutaneous biopsies and drainage (30%; 56% worked in MOH), peripheral arterial interventions (9%; 60% work in the Ministry of Defense), oncology interventions (4%, 50% of them work at King Faisal Specialist Hospital), gastrointestinal/genitourinary interventions (2%) and neuro-interventions (7%). All respondents reported using lead aprons in their practice, 96% (52/54) use thyroid shields, 85% (46/54) used radiation dosimeters and only 48% (26/54) use lead eyeglasses. Other aspects related to clinical practice variations among IR practitioners were also surveyed (Figure 2).

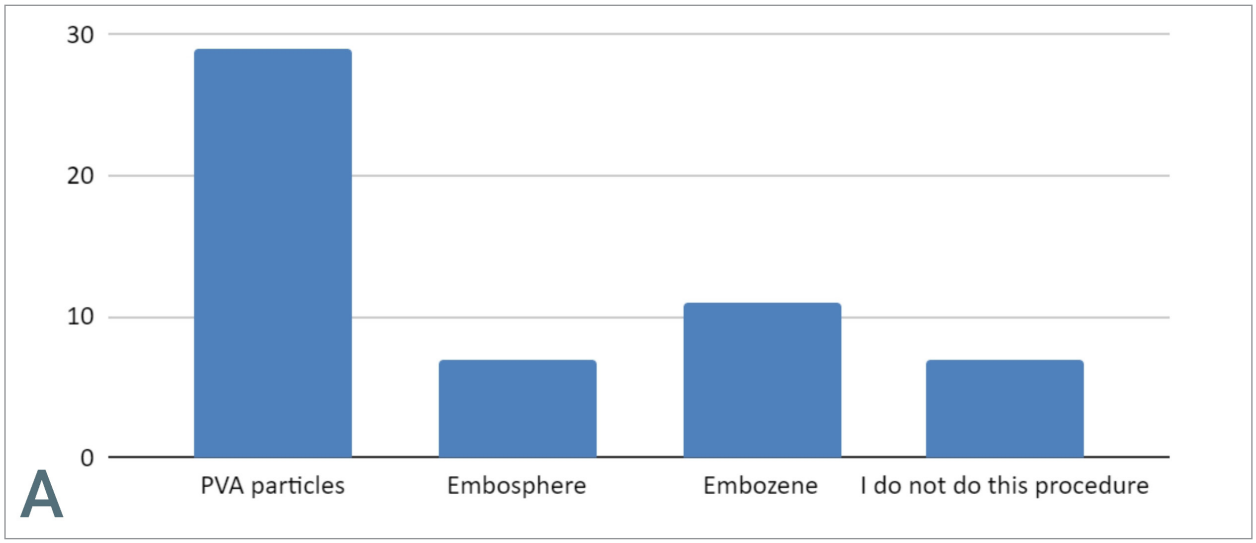
Technical aspects results

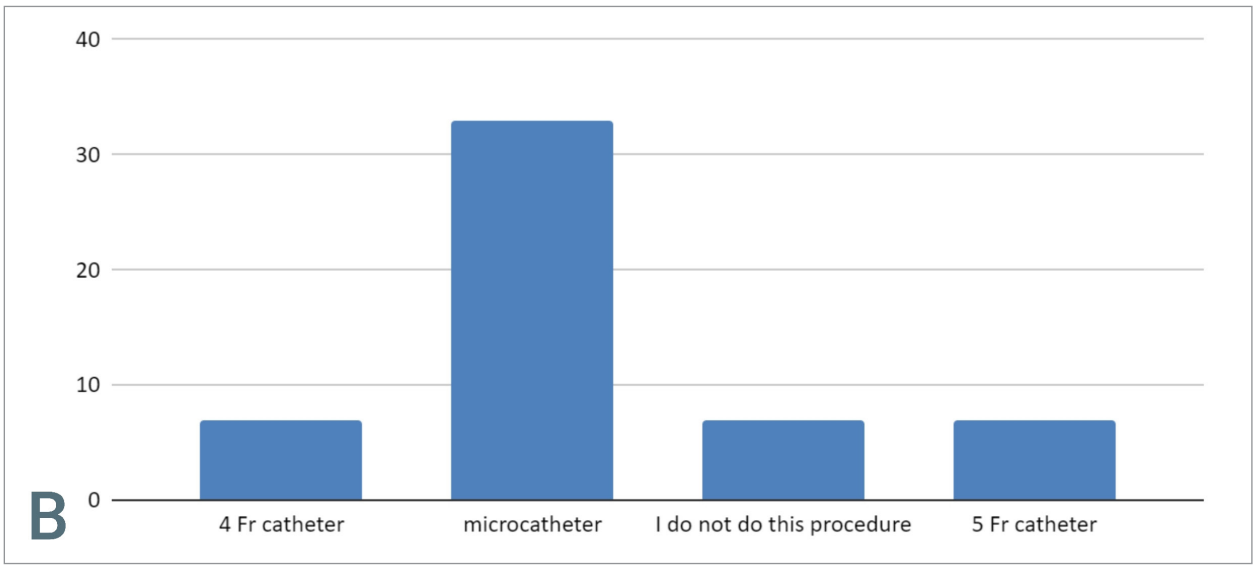
Fifty-four percent of respondents (29/54) reported using local anesthesia for thyroid fine needle aspiration (FNA) procedures, 37% (20/54) do not (9% do not perform this type of procedure), and only 17% (9/54) reported that they request onsite cytology evaluation. Sixty-three percent (34/54) of the respondents use 22-23 gauge (G) needles for thyroid FNA, 28% (15/54) use 24-25G, and no one reported using 26-27G. Other technical variations among IR practitioners in some common procedures, such as uterine fibroid embolization and varicocele embolization, were also surveyed (Figure 3).

Logistics, policies and challenges results

Forty-one percent of the respondents (22/54) reported that endovascular aortic aneurysm repair (EVAR) in their institutions are performed by interventional radiologists and other specialists working as one team, 41% (22/54) reported that it is performed by vascular surgeons, 7% (4/54) reported that it is performed by interventional radiologists and other specialists working as separate teams, and 11% of respondents (6/54) reported that this procedure is not done in their institution. No one reported that EVAR is done by interventional radiologists alone or by cardiologists/cardiovascular surgeons. Approximately forty-five percent of the respondents (24/54) reported that peripheral arterial interventions in their institutions are performed by interventional radiologists alone, 35% (19/54) by interventional radiologists and other specialists as separate teams, 7% (4/54) by interventional radiologists and other specialists as one team, and 13% (7/54) reported that this type of procedure is not done in their institutions. Fifty-four percent of the respondents (29/54) reported that interventional neuroradiology procedures in their institutions are performed by interventional neuroradiologists, 11% (6/54) by interventional neuroradiologists and other specialists as one team, 7% (4/54) by interventional neuroradiologists and other specialists as separate teams, 4% (2/54) by neurosurgeons, 2% (1/54) by neurologists, and 22% (12/54) of the respondents reported that this type of procedure is not done in their institution.

The most frequent challenges and obstacles facing the respondents' IR practices were financial/funding limitation (reported by 26% (14/54); 43% of them work in the MOH), competition and lack of cooperation by other specialties (24% (13/54); 46% work in the MOH), lack of patients and public awareness (17% (9/54); 44% work in the National Guard hospitals), lack of administrative support (11% (6/54), 83% work in the MOH), and shortage of IR doctors and staff (11% (6/54), 50% work in the MOH). Other challenges were reported by 11% (6/54) of respondents.





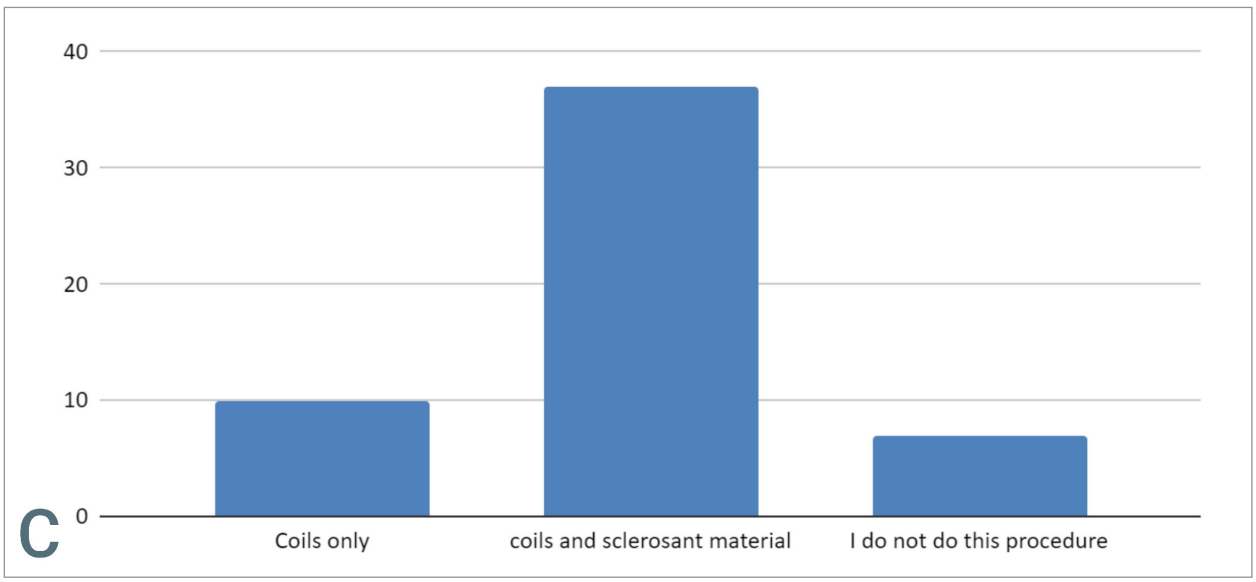


Fig 3: Variations in technical aspects among respondents. A: embolization agents used in UFE. B: type of catheter used in UFE. C: material used in varicocele embolization.

DISCUSSION

The results of this survey provide reference information about IR practice in Saudi Arabia. A literature search showed that this topic was not surveyed previously.

The majority of the respondents were consultants (80%), and yet, the most commonly reported duration of experience was less than 5 years, indicating a young generation of interventional radiologists in this rapidly growing specialty. A clear discrepancy in gender distribution is noted with only 4% females, which appears to be an international issue. In a recent joint survey from the European Society of Radiology and the Cardiovascular and Interventional Radiological Society of Europe (CIRSE), remarkable gender discrepancy was reported, with approximately 28% of the surveyed departments having no female interventional radiologists and 52% of the departments having only 1-25% females out of all interventional radiologists[3]. In the United States in 2005, only 4.7% of those who did interventional fellowships were female[4]. The percentage of women members in the Society of Interventional Radiology was 6% in 2008 and increased to only 13% in 2017[5]**.** A recent study based on a survey by the Pan Arab Interventional Radiology Society concluded that women interventional radiologists face many challenges and are underrepresented in the Arab countries[6]. The reported reasons for this gender discrepancy included concerns of radiation exposure, difficulties in balancing personal and work duties, and a claimed absence of role model female interventional radiologists[3,6].

Diversity of fellowship training was obvious in this survey, with 60% trained in North America and Europe. Despite the relatively recent establishment of Saudi IR fellowship programs, 22% of respondents did their fellowships in Saudi Arabia.

Variations in clinical practice among the respondents were noticeable. Compared to a recent European survey, 52% of respondents in this survey ran IR clinics versus 42% in Europe, and only 19% reported having admission privilege versus 55% in Europe[7]. Certain practices were found not to be following the evidence. For example, pre-procedure antiplatelet therapy (Aspirin) is advisable in all cases of aortoiliac percutaneous endovascular interventions according to the guidelines of CIRSE (level B, class I evidence); however, only 30% of respondents reported practicing that[8]. The evidence is still unclear about the use of dual antiplatelets therapy post-stenting of peripheral arterial disease, and some guidelines recommend against its use; however, 70% of respondents still prescribe dual antiplatelets therapy[8,9].

Wide variations in the techniques of procedures among respondents were present. As an example, thyroid FNA is one of the most commonly performed IR procedures, and yet, there were clear variations in the technical aspects related to this procedure. The majority of respondents (54%) used local anesthesia in thyroid FNA, although several studies do not recommend its routine use, and some studies even found higher pain score when using local anesthesia in a single needle puncture[10,11]. Only 17% of respondents requested onsite cytology evaluation of thyroid FNA, although the importance of rapid onsite evaluation has been confirmed in several studies and can significantly reduce inadequate reports[12,13]. The needle size used for thyroid FNA was mostly the large sizes, 22-23G. Multiple studies have not shown differences in sample adequacy of FNA between small and large needle sizes, even when comparing very large needle sizes (21G) to very small ones (27G)[14,15]. Technical variations among respondents were also present in other commonly performed procedures, such as uterine fibroid embolization (UFE) and varicocele embolization. However, such variations have been reported in different parts of the world, including Europe[16]. Some of those variations can affect the outcome of the procedures, such as the type of embolizing material in UFE and varicocele[17,18].

EVAR is a procedure that can be performed by different specialists. In the United States, the percentage of EVAR procedures completed by vascular surgeons ranges from 66% to 88%[19,20]. In this survey, only 41% of respondents stated that these procedures are performed solely by vascular surgeons in their institutions, while 50% of the respondents stated that EVAR is done by interventional radiologists either independently or as members of a multidisciplinary team. This suggests higher involvement of interventional radiologists in this type of procedure in Saudi Arabia when compared to the United States, although the comparison depends on the percentage of respondents rather than the percentage of procedures, as the latter parameter is not available for analysis in this study. However, it was not reported in this survey that there are institutions in which EVAR is done exclusively by interventional radiologists. On the other hand, a much higher involvement (87%) of interventional radiologists has been reported in peripheral arterial disease interventions, out of which 44% are done exclusively by interventional radiologists. This higher involvement of interventional radiologists in peripheral vascular interventions is also reported in Europe, with a vast majority (81%) of interventional radiologists performing peripheral

arterial interventions, followed by vascular surgeons (58%), cardiologists (19%) and angiologists (13%)[7]. A recent study from the United States showed that the greatest proportional increase (by about 107%) in infra-popliteal claims for the period of 2011 to 2017 occurred among interventional radiologists[21].

There are several challenges facing the IR specialists, including financial limitations, lack of cooperation by other specialists, lack of public awareness, deficiency in administrative support and staff shortages. These challenges seem to vary among different healthcare sectors. In the MOH sector, the most commonly reported challenges were financial limitations, lack of cooperation by other specialties and lack of administrative support. In the National Guard health affairs sector, the most commonly reported challenge was the lack of public and patient awareness of IR. Similar and other challenges were also reported in different parts of the world, including the United States, Europe and Canada[3,22,23].

A response rate of only 56% is a limitation in this study, although it is still higher than the rate reported in several similar international studies[22,23].

CONCLUSION

This study presents an overview of the current status of IR practice in Saudi Arabia. Variations in clinical practice and technical aspects among interventional radiologists were observed. Several challenges and obstacles were reported.

Bringing attention to these findings and conducting similar studies to investigate the IR status in other countries is one of the messages of this study. Recommendations can be made to the different societies of interventional radiology, including the Saudi Interventional Radiology Society, to come up with practice guidelines to unify certain aspects of IR practice. Collaboration among all stakeholders at multiple levels in all healthcare sectors is also recommended to overcome several reported challenges related to IR practice in Saudi Arabia and worldwide.

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Conflicts of interest: None

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REFERENCES

1. Doherty MG. Value of interventional radiology: past, present, and future. Semin Intervent Radiol 2019; 36(1):26-8.
2. Al-Hanawi MK, Khan SA, Al-Borie HM. Healthcare human resource development in Saudi Arabia: emerging challenges and opportunities-a critical review. Public Health Rev 2019; 40:1.
3. European Society of Radiology (ESR), Cardiovascular and Interventional Radiological Society of Europe (CIRSE). Interventional radiology in European radiology departments: a joint survey from the European Society of Radiology (ESR) and the Cardiovascular and Interventional Radiological Society of Europe (CIRSE). Insights Imaging 2019; 10(1):16.
4. Sunshine JH, Lewis RS, Bhargavan M. A portrait of interventional radiologists in the United States. AJR Am J Roentgenol 2005; 185(5):1103-12.
5. Wang M, Laguna B, Koethe Y, Lehrman E, Kumar V, Kohi MP. Bridging the gender gap in the society of IR: A benchmark study. J Vasc Interv Radiol 2019; 30(4):584-588.e2.
6. Khafagy RTM, Abd El Tawab KA, Hammami N, Bouklata S, Findeiss L, Arabi M. Experience of women in IR in the Arab World: Survey by the Pan Arab Interventional Radiology Society. J Vasc Interv Radiol 2020; 31(7):1158-1163.e2.
7. Kok HK, Rodt T, Fanelli F, Hamady M, Müller-Hülsbeck S, Santiago MC, *et al*. Clinical and endovascular practice in interventional radiology: a contemporary European analysis. CVIR Endovasc 2018; 1(1):8.
8. Rossi M, Iezzi R. Cardiovascular and Interventional Radiological Society of Europe guidelines on endovascular treatment in aortoiliac arterial disease. Cardiovasc Intervent Radiol 2014; 37(1):13-25.
9. Alonso-Coello P, Bellmunt S, McGorrian C, Anand SS, Guzman R, Criqui MH, *et al*. Antithrombotic therapy in peripheral artery disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):e669S-e690S.
10. Lee YH, Baek JH, Jung SL, Kwak JY, Kim J-H, Shin JH, *et al*. Ultrasound-guided fine needle aspiration of thyroid nodules: a consensus statement by the Korean Society of Thyroid Radiology. Korean J Radiol 2015; 16(2):391-401.
11. Kim DW, Rho MH, Kim KN. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules: is it necessary to use local anesthesia for the application of one needle puncture? Korean J Radiol 2009; 10(5):441-6.
12. Shield PW, Cosier J, Ellerby G, Gartrell M, Papadimos D. Rapid on-site evaluation of fine needle aspiration specimens by cytology scientists: a review of 3032 specimens. Cytopathology 2014; 25(5):322-9.
13. Witt BL, Schmidt RL. Rapid onsite evaluation improves the adequacy of fine-needle aspiration for thyroid lesions: a systematic review and meta-analysis. Thyroid 2013; 23(4):428-35.
14. Al-Damegh SA. Ultrasound guided fine needle aspiration using 25G needle as a new technique for a wide range of pathological conditions. Saudi Med J 2004; 25(10):1374-7.
15. Gumus M, Cay N, Algin O, Ipek A, Ersoy RU, Belenli O, *et al*. Comparison of 21 and 27 gauge needles for determining sample adequacy in the aspiration biopsy of thyroid nodules. Diagn Interv Radiol 2012; 18(1):102-5.

16. Voogt MJ, Arntz MJ, Lohle PNM, Mali WPM, Lampmann LEH. Uterine fibroid embolisation for symptomatic uterine fibroids: a survey of clinical practice in Europe. Cardiovasc Intervent Radiol 2011; 34(4):765-73.
17. Das R, Champaneria R, Daniels JP, Belli A-M. Comparison of embolic agents used in uterine artery embolisation: a systematic review and meta-analysis. Cardiovasc Intervent Radiol 2014; 37(5):1179-90.
18. Reiner E, Pollak JS, Henderson KJ, Weiss RM, White RI Jr. Initial experience with 3% sodium tetradecyl sulfate foam and fibered coils for management of adolescent varicocele. J Vasc Interv Radiol 2008; 19(2 Pt 1):207-10.
19. Hurks R, Ultee KHJ, Buck DB, DaSilva GS, Soden PA, van Herwaarden JA, *et al*. The impact of endovascular repair on specialties performing abdominal aortic aneurysm repair. J Vasc Surg 2015; 62(3):562-568.e3.
20. Dua A, Andre J, Nolte N, Pan J, Hood D, Hodgson KJ, *et al*. The impact of physician specialization on clinical and hospital outcomes in patients undergoing EVAR and TEVAR. Ann Vasc Surg 2016; 35:138-46.
21. Schramm KM, DeWitt PE, Dybul S, Rochon PJ, Patel P, Hieb RA, *et al*. Recent trends in clinical setting and provider specialty for endovascular peripheral artery disease interventions for the Medicare population. J Vasc Interv Radiol 2020; 31(4):614-621.e2.
22. Kennedy SA, Abraham RJ, Mujoomdar A, Valenti DA, Klass D, Wong JK. Interventional radiology in Canada: Current challenges and future directions. AJR Am J Roentgenol 2018; 211(4):736-9.
23. Cook PS. The challenges of providing interventional radiology services to rural and smaller community hospitals. AJR Am J Roentgenol 2018; 211(4):744-7.

Original Article

HLA class I and class II polymorphism in mitral chordae tendineae rupture

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ABSTRACT

Objective: Mitral chordae tendinea rupture (MCTR) is a progressive condition which frequently results in severe mitral regurgitation. Several studies have suggested that genetic susceptibility to various valvular heart diseases is linked to human leukocyte antigen (HLA) alleles. The aim of the present study was to evaluate the significance of polymorphisms in HLA class I and class II genes in patients with MCTR.
Design: Prospective study
Setting: Sakarya University Training and Research Hospital, Sakarya, Turkey
Subjects: Twenty-one patients with primary MCTR and 147 age and sex matched controls were enrolled in the study.
Interventions: Five milliliters of fasting venous blood obtained from each participant and stored in ethylenediaminetetraacetate tubes
Main outcome measure: HLA alleles were analyzed using sequence specific primer-polymerase chain reaction and nucleotide sequencing.
Results: Compared to the control group, patients with MCTR had an increased frequency of HLA-A2, HLA-A3, HLA-A24, HLA B-7, HLA B35, HLA-DR4, HLA-DR7 and HLA-DR15 alleles. Furthermore, an independent association was found between MCTR and of HLA-A3, HLA-A24, HLA-B35 and HLA-DR4 haplotypes.
Conclusion: The current study is the first to describe distinct HLA allele frequency in patients with MCTR. Further studies including a greater number of patients are needed to examine the causal effects of HLA on MCTR.

KEY WORDS: human leukocyte antigen, mitral chordae tendineae

INTRODUCTION

Mitral chordae tendineae rupture (MCTR) is an important cause of severe mitral regurgitation (MR) and leads to 6.6-8.1% of all valvular surgeries[1]. It is a progressive condition that may eventually require mitral valve surgery, since MCTR patients have a high (6.3%) mortality rate when treated medically. Therapeutic decisions are made according to the severity of MR and clinical symptoms. The vast majority of patients with MCTR experience separation of multiple chords, which leads to severe MR and requires immediate surgical intervention[2]. Various disease processes have been linked to the development of MCTR, including mitral valve prolapse, local myxomatous degeneration, rheumatic heart disease, sub-acute endocarditis, hypertrophic cardiomyopathy, connective tissue disease (such as Marfan and Ehler-Danlos syndrome) and Kawasaki disease. However, in a significant proportion of patients, no specific cause of MCTR could be identified, and is thus referred to as 'primary MCTR'[3-5].

An early diagnosis of this condition and the determination of associated risk factors may increase survival rates[2,6]. Therefore, understanding the pathogenesis and identification of individual susceptibility to MCTR is essential for risk modification. The histopathologic studies indicated that increased expression of genes encoding signal

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cascade that instigate cardiac remodeling and fibrosis, inflammation and abnormal humoral and cellular immune response has been proposed as a potential cause of MCTR. This inflammatory reaction includes the activation of inflammatory cells positive for CD11b and CD14, inflammatory cells secreting matrix metalloproteinases and cytokines[7,8]. Although inflammation and genetic susceptibility might play a possible role, the exact pathophysiological mechanism of MCTR is not clear.

Genes encoding human leukocyte antigen (HLA) are a critical component of immunoregulation and inflammation. HLA antigens interact with T lymphocytes and natural killer cells and trigger local inflammation by secretion of cytokines, which play an important role in cardiac fibrosis and inflammation[9,10]. The relationship between HLA and various valvular disorders such as rheumatic heart disease (RHD), degenerative aortic stenosis and mitral valve prolapse (MVP) has been demonstrated in previous studies[10-17]. Rheumatic valvular heart disease and myxomatous mitral valve disease are well-known predisposing factors in MCTR. Based on the above observations of the altered expression of HLA alleles in these diseases, we intended to investigate HLA allele frequency in patients with MCTR. Accordingly, we hypothesized that the polymorphism of HLA alleles may influence individual susceptibility to MCTR.

SUBJECTS AND METHODS

Patient population

The study was performed as a matched case control study conducted at the Sakarya University School of Medicine. Twenty-one patients with primary MCTR and 147 controls were enrolled in the study. Primary MCTR is defined as a case in which there was neither a recognized, reasonable and probable cause nor a prior structural cardiac abnormality such as rheumatic valvular disease and myxomatous valve degeneration. Patients with acute myocardial infarction, hypertrophic cardiomyopathy, or prior history of infective endocarditis, RHD, connective tissue disease, blunt chest trauma and chronic-active inflammatory disease were also excluded from the study. The control group consisted of 147 asymptomatic hospital staff including doctors, nurses and technicians without valvular heart disease, matched for age and gender. Transthoracic echocardiography was performed in all study participants according to the recommendations of American Society of Echocardiography. Diagnosis of MCTR was based on standard echocardiographic methods. Echocardiographic determinants included incomplete leaflet coaptation and rapid systolic movement of the involved leaflet tip into the left atrium. All the subjects in MCTR group underwent transesophageal echocardiography to confirm the diagnosis. Ethical approval for this study was provided by the Ethical Committee of Sakarya University School of Medicine. The study conformed to the ethical principles of the Declaration of Helsinki. Informed written consent was obtained from each subject included in the present study.

Sample preparation and genomic DNA extraction

Five milliliters of venous blood was obtained from each participant and stored in ethylenediaminetetraacetate (EDTA) tubes. DNA extraction for molecular typing was performed using extraction columns (QIAamp DNA mini kit, Qiagen). HLA typing for HLA class I (HLA-A and HLA-B) and class II (HLA-DR) were performed using polymerase chain reaction with sequence-specific primers (PCR-SSP) (low resolution Olerup SSP® HLA Typing Kits) according to the manufacturer's instructions. The incubation process of the thermocycle of the PCR (Sensoquest PCR systems, Germany) was performed as follows: 1 cycle at 94°C for 2 minutes and 10 cycles at 94°C for 10 seconds and at 65°C for 60 seconds, 20 cycles at 94°C for 10 seconds and at 61°C for 50 seconds, and a final extension at 72°C for 30 seconds. Total reaction volume in each well was 10 μl. Using these protocols, we analyzed *01, *02, *03, *11, *23, *24, *25, *26, *29, *30, *31, *32, *33, *34, *36, *43, *66, *68, *69, *74 and *80 alleles in HLA-A; *07, *08, *13, *14, *15, *18, *27, *35, *37, *38, *39, *40, *41, *42, *44, *45, *46, *47, *48, *49, *50, *51, *52, *53, *54, *55, *56, *57, *58, *59, *67, *73, *78, *81, *82 and *83 alleles in HLA-B and *01, *03, *04, *07, *08, *09, *10, *11,*12, *13, *14, *15, and *16 alleles in HLA-DR group.

The PCR products were separated by agarose gel electrophoresis (2%) in Tris-Borate-EDTA buffer (90 mM Tris base, 90 mM boric acid, 2 mM EDTA) 0.5 M 20 mL; distilled water to 1000 mL, at 100 volts for 1 hour at room temperature. Amplicons in the gel were stained with ethidium bromide (0.5 μg/mL). Gels were visually analysed under an ultraviolet light.

Statistical analysis

Analyses were performed using commercial software (IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.). Descriptive analyses were performed to provide information on general characteristics of the study population. Categorical variables were presented as counts and percentages. Kolmogorov-Smirnov test was used to evaluate whether the distributions of continuous variables were normal. All the variables displayed normal distribution and presented as the means ± standard deviation. Independent samples t test was used to compare the age between study and control groups. Categorical variables were compared

by Chi-square test. A multivariate logistic regression model was implemented to determine HLA subgroups associated with MCTR. A *P*-value of less than 0.05 was considered significant.

RESULTS

Demographic and laboratory data of MCTR and control group are summarized in Table 1. The mean age of the MCTR group and control group was 57±16 and 55±10 years respectively (*P*=0.497). Clinical and laboratory data were both similar between groups.

Table 1: Demographic and clinical characteristics

Variables	Control (n=147)	MCTR (n=21)	*P*
Age	54.50±9.98	57.00±16.12	0.497
Gender (Male)	99 (67.3)	14 (66.7)	1.000
Hypertension	64 (43.5)	8 (38.1)	0.814
Diabetes mellitus	12 (8.2)	1 (4.8)	1.000
Coronary artery disease	12 (8.2)	1 (4.8)	1.000
Creatinine (mg/dl)	0.87±0.16	0.96±0.38	0.29
CRP (mg/l)	3.88±2.06	4.57±2.82	0.35

Data were shown as count (percentage) and mean ± standard deviaton.
CRP: C-reactive protein

A total of 118 alleles obtained from the MCTR group and 535 alleles obtained from the control group were evaluated. Table 2 displays the results of HLA class I and class II allelic frequencies between the groups. We found a higher frequency of HLA-A2 (38% vs. 13%, *P*=0.008), HLA-A3 (33% vs. 9%, *P*=0.007), HLA-A24 (38% vs. 9%, *P*=0.001), HLA B-7 (19% vs. 4%, *P*=0.02), HLA B35 (43% vs. 13%, *P*=0.003), HLA-DR4 (33% vs. 11%, *P*=0.01), HLA-DR7 (29% vs. 10%, *P*=0.04) and HLA-DR15 (24% vs. 5%, *P*=0.008) alleles in MCTR group as compared to control group.

Multivariate stepwise logistic regression analysis was used to determine the variables most strongly associated with MCTR. The analysis was applied to the selected variables including HLA-A2, HLA-A3, HLA-A24, HLA-B7, HLA-B35, HLA-DR4, HLA-DR7 and HLA-DR-15. In this analysis, higher expression of HLA-A3 (OR=12.606, 95% CI: 3.049 to 52.117, *P*<0.001), HLA-A24 (OR=8.495, 95% CI: 1.954 to 36.929, *P*=0.004), HLA-B35 (OR=4.920, 95% CI: 1.407 to 14.208, *P*=0.013), HLA-DR4 (OR=7.967, 95% CI: 1.911 to 33.218, *P*=0.004), alleles were independently associated with the occurrence of MCTR (Table 3).

DISCUSSION

Currently, no published reports have been made available on the HLA expression profile of MCTR. To our knowledge, this is the first study showing different frequencies of certain HLA alleles in patients with MCTR as compared to control. The expression of 8 HLA alleles were significantly higher in the MCTR group.

Table 2: Comparison results of the HLA subgroups between control and MCTR groups.

HLA subgroups	Control (n=147)	MCTR (n=21)	*P*
A1	19 (12.9)	3 (14.3)	0.741
A2	19 (12.9)	8 (38.1)	0.008
A3	14 (9.5)	7 (33.3)	0.007
A11	14 (9.5)	2 (9.5)	1.000
A23	15 (10.2)	3 (14.3)	0.475
A24	13 (8.8)	8 (38.1)	0.001
A26	12 (8.2)	2 (9.5)	0.688
A29	12 (8.2)	1 (4.8)	1.000
A30	13 (8.8)	2 (9.5)	1.000
A32	16 (10.9)	1 (4.8)	0.699
A68	14 (9.5)	1 (4.8)	0.696
A69	9 (6.1)	0 (.0)	0.604
B7	6 (4.1)	4 (19.0)	0.023
B8	10 (6.8)	0 (.0)	0.615
B13	8 (5.4)	2 (9.5)	0.363
B14	6 (4.1)	1 (4.8)	1.000
B15	11 (7.5)	1 (4.8)	1.000
B18	9 (6.1)	3 (14.3)	0.176
B27	10 (6.8)	2 (9.5)	0.648
B35	20 (13.6)	9 (42.9)	0.003
B37	7 (4.8)	1 (4.8)	1.000
B39	9 (6.1)	1 (4.8)	1.000
B40	4 (2.7)	1 (4.8)	0.492
B44	11 (7.5)	3 (14.3)	0.388
B49	16 (10.9)	3 (14.3)	0.711
B50	8 (5.4)	0 (.0)	0.598
B51	14 (9.5)	3 (14.3)	0.450
B52	7 (4.8)	2 (9.5)	0.313
B54	7 (4.8)	0 (.0)	0.598
B55	8 (5.4)	1 (4.8)	1.000
B57	5 (3.4)	1 (4.8)	0.557
B58	8 (5.4)	1 (4.8)	1.000
DR1	10 (6.8)	4 (19.0)	0.078
DR3	14 (9.5)	1 (4.8)	0.696
DR4	17 (11.6)	7 (33.3)	0.015
DR7	15 (10.2)	6 (28.6)	0.029
DR8	12 (8.2)	1 (4.8)	1.000
DR10	13 (8.8)	1 (4.8)	1.000
DR11	29 (19.7)	7 (33.3)	0.163
DR12	12 (8.2)	1 (4.8)	1.000
DR13	20 (13.6)	3 (14.3)	1.000
DR14	12 (8.2)	2 (9.5)	0.688
DR15	7 (4.8)	5 (23.8)	0.008
DR16	12 (8.2)	1 (4.8)	1.000

Data were shown as count (percentage).
MCTR: mitral chordae tendinea rupture

HLA antigens were initially identified on the surface of immunocompetent cells such as monocytes/macrophages, T and B lymphocytes which were responsible for the regulation of the cellular immune response by the presentation of foreign antigens[18]. However, aberrant expression of HLA alleles on cells not considered part of the immune system have been found to be associated with several autoimmune disorders. The best evidence of this phenomenon

Table 3: Logistic regression models for the MCTR and independent risk factors

HLA subgroups	β	SE of β	*P*	OR	CI for OR
A3	2.534	0.724	<0.001	12.606	3.049-52.117
A24	2.140	0.750	0.004	8.495	1.954-36.929
B7	2.163	1.121	0.054	8.697	0.966-78.282
B35	1.593	0.639	0.013	4.920	1.407-17.208
DR4	2.075	0.728	0.004	7.967	1.911-33.218
DR7	1.449	0.772	0.060	4.258	0.938-19.329
DR15	1.855	0.976	0.057	6.392	0.943-43.331

β: regression coefficient, SE: standard error, CI: confidents interval; OR: odds ratio; HLA: human leukocyte antigen

may be HLA-DR expression by thyrocytes in Graves' disease, which has been found to play an essential role in the initiation and progression of the disease process[19]. Moreover, aberrant expression of HLA has been detected on fibroblasts in progressive systemic sclerosis[20], on smooth muscle cells in atherosclerotic plaques[21], and on epithelial cells in Crohn's disease[22]. These studies revealed that aberrant expression of HLA on non-immunocompenent cells promote T cells to initiate autoimmune attack, resulting in the direct destruction of local tissue[23].

HLA antigens have also been shown to be expressed on valvular tissues. It has been suggested that local aberrant expression of HLA antigens by valvular epithelial cells and fibroblasts stimulate T cells to initiate autoantibody production, leading to the direct destruction of valvular tissue apparatus[10,11]. Olsson *et al* showed aberrant expression of HLA-DR on the endothelial surface of the leaflets and fibroblast like cells in the fibrosa and spongiosa in patients with degenerative aortic stenosis[10]. A study by Johnson *et al* also demonstrated that human valve endothelial cells can cause the allostimulation of PBMC and resting CD4+ T cells. They revealed that the response of CD4+ T cells was dependent on HLA Class II expression[24]. Amoils *et al* revealed aberrant expression of HLA-DR by the fibroblasts of the valvular tissue of the patients with acute rheumatic fever[25]. There was no study investigating aberrant expression of HLA by valvular tissue cells in MCTR. In the present study, we evaluated circulating HLA expression in patients with MCTR. The use of whole-blood preparations for the HLA analyses, as in the case of our study, may not provide a specific source of HLA expression. However, higher frequency of circulating HLA alleles might be the result of tissue-level aberrant HLA expression.

Several investigators have attempted to analyze the association between HLA alleles and circulating whole blood cells with various valvular heart diseases. A study by Ozkan *et al* showed that susceptibility to RHD in Turkish patients is mainly class II and weakly class I mediated, with B16, DR3 and DR7 influencing susceptibility and DR5 conferring protection[14]. A study by Okello also demonstrated that there was a significant association of HLA-DR11 in patients with RHD, whereas the risk was lower in HLA-DR1 positive patients[15]. In the other studies performed in patients with RHD, HLA-A29, -A30, -A31, -A3, -B7, -B8, -B22, -B5; -B18 and -B35 were proposed as susceptibility markers to the development of RHD. Conversely, a protective role of HLA-B49 and B52 alleles were also reported[12,16,17,26]. We observed that higher expression of HLA A3 and B35 alleles were independently associated with the MCTR. Thus, the expression profile of these HLA alleles could potentially be involved in the development of MCTR as well as RHD.

The relationship between HLA alleles and MVP linked to development of the MCTR has also been investigated in a few studies. A study conducted by Filipenko showed that patients with MVP have an increased expression of B35 antigen of HLA system, which causes dysmetabolism of collagen in the mitral cusps[27]. In another study, higher frequency for HLA-B15 and HLA-B35 alleles have also been reported in patients with MVP[13]. In our study, we also demonstrated higher HLA-B35 expression in patients with MCTR which deserves attention, considering the link between MVP and MCTR.

Underlying mechanistic role of HLA alleles on development of MCTR have primarily focused on matrix metalloproteinase metabolism. Previously, Kimura *et al* showed that the up-regulation of matrix metalloproteinase (MMP) 1, MMP 2, MMP 9 and MMP 13, likely plays a major role in the molecular mechanism underlying the pathophysiology of MCTR[7]. In addition, Lin *et al* have shown that MMP 1 gene expression and MMP 1-1607 16/26 gene polymorphism were independently linked with MCTR[8]. The results of these studies have indicated that MMP expression might trigger a signal cascade that instigates cardiac remodeling and fibrosis, as well as a predisposition to MCTR. An association between soluble HLA alleles and MMP expressions was investigated in a few reports. Trayssac *et al* firstly demonstrated that both anti-HLA class I and II antibodies activate a stress-induced signaling pathway implicating MMP in patients with transplant vasculopathy[28]. Galvani *et al* also reported that anti-HLA antibodies are mitogenic for smooth muscle cells through a signaling mechanism implicating membrane type 1 MMP and MMP2[29]. Furthermore, Rizzo *et al* suggested an effective link between MMP-2 and HLA-G1, which is a non-classical HLA class I antigen[30]. Although it is plausible to hypothesize that activations of certain MMPs induced by HLA

alleles might play potential roles in development of MCTR, this issue was not specifically investigated in our study.

Limitations of the study

This study has some limitations. The major limitation of the present study is its small sample size. The second limitation is related to ethnic heterogeneity of expression of HLA alleles in various populations. Since ethnic differences may influence the distribution of HLA alleles, a lack of diversity may complicate efforts to extrapolate our results to other ethnic groups. Third, while this genetic study has established an association between HLA alleles and MCTR, the precise function of HLA alleles on MCTR development has not been fully elucidated. Thus, rather than being a direct pathogenic cause of MCTR, HLA polymorphism could merely be used as a marker of predisposition. Therefore, although the results of our study are interesting, they should be cautiously interpreted until further studies with a greater number of patients and different ethnic populations are conducted.

CONCLUSION

In this first study of the association between the HLA class I and II expression and MCTR, we propose that specific HLA alleles such as HLA-A2, HLA-A3, HLA-A24, HLA B-7, HLA B35, HLA-DR4, HLA-DR7 and HLA-DR15 may be involved in development of MCTR. Further studies identifying predisposing factors and genes for the development of MCTR may enhance understanding of pathophysiologic basis of MCTR.

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Author contribution: Mehmet Bulent Vatan planned the methodology and wrote the manuscript; Aysel Kalayci Yigin took responsibility in collection of relevant biological materials, data management and reporting collected data; Ramazan Akdemir constructed the hypothesis of article; Mustafa Tarik Agac took responsibility in statistical interpretation and conclusion of the results; Asli Vatan reviewed the article before submission scientifically besides spelling and grammar, and edited the manuscript; Keziban Karacan provided access to crucial research components (personnel, equipment, environment), and took responsibility in ethical approval process.
Conflict of interest: None

REFERENCES

1. Gabbay U, Yosefy C. The underlying causes of chordae tendinae rupture: a systematic review. Int J Cardiol 2010; 143(2):113-8.
2. Ling LH, Enriquez-Sarano M, Seward JB, Tajik AJ, Schaff HV, Bailey KR, *et al*. Clinical outcome of mitral regurgitation due to flail leaflet. N Engl J Med 1996; 335(19):1417-23.
3. Oliveira DB, Dawkins KD, Kay PH, Paneth M. Chordal rupture. I: aetiology and natural history. Br Heart J 1983; 50(4):312-7.
4. Tsukasa TT, Sakaguchi H, Kitano M, Kurosaki K, Shiraishi I, Kagizaki K, *et al*. Clinical characteristics of acute regurgitation due to ruptured chordae tendineae in infancy-experience at a single institution. Eur J Pediatr 2012; 171:259-65.
5. Hickey AJ, Wilcken DE, Wright JS, Warren BA. Primary (spontaneous) chordal rupture: relation to myxomatous valve disease and mitral valve prolapse. J Am Coll Cardiol 1985; 5(6):1341-6.
6. Mills WR, Barber JE, Ratliff NB, Cosgrove 3rd DM, Vesely I, Griffin BP. Biomechanical and echocardiographic characterization of flail mitral leaflet due to myxomatous disease: further evidence for early surgical intervention. Am Heart J 2004; 148(1):144-50.
7. Kimura N, Shukunami C, Hakuno D, Yoshioka M, Miura S, Docheva D, *et al*. Local tenomodulin absence, angiogenesis, and matrix metalloproteinase activation are associated with the rupture of the chordae tendineae cordis. Circulation 2008; 118(17):1737-47.
8. Lin TH, Yang SF, Chiu CC, Su HM, Wang CL, Voon WC, *et al*. Matrix metalloproteinase-1 mitral expression and -1607 1G/2G gene promoter polymorphism in mitral chordae tendinae rupture. Transl Res 2013; 161(5):406-13.
9. Janeaway CA. The major histocompatibility complex and its functions. In: Immunobiology: The Immune System in Health and Disease. 5th ed. New York: Garland Science; 2001.
10. Olsson M, Rosenqvist M, Nilsson J. Expression of HLA-DR antigen and smooth muscle cell differentiation markers by valvular fibroblasts in degenerative aortic stenosis. J Am Coll Cardiol 1994; 24(7):1664-71.
11. Ward C, Gelsthorpe K, Doughty RW. A relation between HLA antigens and clinical features in patients with acquired valvular heart disease. Br Med J 1976; 1(6024):1499-501.
12. El-Hagrassy N, El-Chennawi F, Zaki M, Fawzy H, Zaki A, Joseph N. HLA class I and class II HLA DRB profiles in Egyptian children with rheumatic valvular disease. Pediatr Cardiol 2010; 31(5):650-6.
13. Kontopoulos A, Harsoulis P, Adam K, Papadopoulos G, Polymenidis Z, Boudoulas H. Frequency of HLA antigens in Graves' hyperthyroidism and mitral valve prolapse. J Heart Valve Dis 1996; 5(5):543-7.
14. Ozkan M, Carin M, Sönmez G, Senocak M, Ozdemir M, Yakut C. HLA antigens in Turkish race with rheumatic heart disease. Circulation 1993; 87(6):1974-8.
15. Okello E, Beaton A, Mondo CK, Kruszka P, Kiwanuka N, Odoi-Adome R, *et al*. Rheumatic heart disease in Uganda: the association between MHC class II HLA DR alleles and disease: a case control study. BMC Cardiovasc Disord 2014; 14:14-28.

16. Gündogdu F, Islamoglu Y, Pirim I, Gurlertop Y, Dogan H, Arslan S, *et al*. Human leukocyte antigen (HLA) class I and II alleles in Turkish patients with rheumatic heart disease. J Heart Valve Dis 2007; 16(3):293-9.
17. Haydardedeoğlu FE, Tutkak H, Köse K, Düzgün N. Genetic susceptibility to rheumatic heart disease and streptococcal pharyngitis: association with HLA-DR alleles. Tissue Antigens 2006; 68(4):293-6.
18. Benacerraf B. Role of MHC gene products in immune regulation. Science 1981; 212(4500):1229-38.
19. Park MH, Park YJ, Song EY, Park H, Kim TY, Park DJ, *et al*. Association of HLA-DR and -DQ genes with Graves' disease in Koreans. Hum Immunol 2005; 66:741-7.
20. Arnett FC. HLA and autoimmunity in scleroderma (systemic sclerosis). Int Rev Immunol 1995; 12(2-4):107-28.
21. Stemme S, Fager G, Hansson GK. MHC class II antigen expression in human vascular smooth muscle cells is induced by interferon-gamma and modulated by tumor necrosis factor and lymphotoxin. Immunology 1990; 69(2):243-9.
22. Mahdi BM. Role of HLA typing on Crohn's disease pathogenesis. Ann Med Surg (Lond) 2015; 4(3):248-53.
23. Bottazzo GF, Pujol-Borrell R, Hanafusa T, Feldmann M. Role of aberrant HLA-DR expression and antigen presentation in induction of endocrine autoimmunity. Lancet 1983; 2(8359):1115-9.
24. Johnson DL, Rose ML, Yacoub MH. Immunogenicity of human heart valve endothelial cells and fibroblasts. Transplant Proc 1997; 29(1-2):984-5.
25. Amoils B, Morrison RC, Wadee AA, Marcus R, Ninin D, King P, *et al*. Aberrant expression of HLA-DR antigen on valvular fibroblasts from patients with active rheumatic carditis. Clin Exp Immunol 1986; 66(1):88-94.
26. Naito S. HLA and disease-heart valvular disease and aortitis syndrome. Jap J Med 1980; 19:66-68
27. Filipenko PS, Malookaia IS. [The role of connective tissue dysplasia in the forming of mitral valve prolapse.] Klin Med (Mosk) 2006; 84(12):13-9. Article in Russian.
28. Trayssac M, Nègre-Salvayre A, Thomsen M. Mechanisms of human smooth muscle cell proliferation and transplant vasculopathy induced by HLA class I antibodies: in vitro and in vivo studies. Hum Immunol 2012; 73(12):1253-60.
29. Galvani S, Trayssac M, Augé N, Thiers JC, Calise D, Krell HW, *et al*. A key role for matrix metalloproteinases and neutral sphingomyelinase-2 in transplant vasculopathy triggered by anti-HLA antibody. Circulation 2011; 124(24):2725-34.
30. Rizzo R, Trentini A, Bortolotti D, Manfrinato MC, Rotola A, Castellazzi M, *et al*. Matrix metalloproteinase-2 (MMP-2) generates soluble HLA-G1 by cell surface proteolytic shedding. Mol Cell Biochem 2013; 381(1-2):243-55.

Original Article

The effect of non-dipper hypertension on contrast-induced nephropathy in coronary artery disease

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ABSTRACT

Objectives: This study aimed to evaluate non-dipper hypertension for risk of contrast-induced nephropathy in patients with coronary artery disease undergoing percutaneous coronary intervention.
Design: Prospective study
Setting: Department of Cardiology, Erciyes University Medical Faculty
Subject: This study prospectively included a total of 161 patients (108 patients with dipper, 53 with non-dipper). Blood pressure (BP) measurements in the clinic were performed using sphygmomanometer. If the mean BP measured during night wass less than 10% lower than the mean daytime measurement, these individuals were "non-dipper".
Intervention: Negative efficacy of non-dipper hypertension on renal
Main Outcome Measure: Patients were evaluated as contrast-induced nephropathy according to 25% increase creatinine level.
Results: When both groups were compared for the development of contrast-induced nephropathy, it was detected in 11 (20%) patients in the non-dipper group and in 8 (7%, *P*=0.016) patients in the dipper group. Mehran risk scoring predictor of contrast nephropathy revealed a significant difference between hypertension and diabetes mellitus (DM) in the groups, except for non-dipper hypertension (P=0.016 and *P*=0.028, respectively). The effect of non-dipper hypertension was significant in multivariant analysis among the parameters affecting contrast nephropathy (*P*=0.023, OR: 0.99-7.984).
Conclusions: Non-dipper hypertension is a risk factor in the development of contrast-induced nephropathy, independently of the risk factors of the Mehran.

KEY WORDS: coronary artery disease, CIN, Mehran, non-dipper hypertensions

INTRODUCTION

The gold standard in determination of coronary artery disease (CAD) is still coronary angiography. Agents used for coronary angiography are ionic substances which are not so innocent. Called as contrasting agents, these substances may cause a range of side effects from allergic events to contrast-induced nephropathy (CIN).

Contrast induced nephropathy is an important complication of invasive cardiovascular procedures. Patients with CAD have a higher risk of developing CIN after percutaneous coronary intervention (PCI)[1].

The development of CIN is a major determinant of short- and long-term morbidity and mortality in patients with CAD, despite successful PCI[2,3]. Although the pathophysiologic mechanisms of development of CIN are complex and multi-factorial, probable mechanisms include intra-renal vasoconstriction, reduced renal blood flow, oxidative stress, inflammation, endothelial dysfunction, and direct tubular epithelial cell injury by contrast media[4].

Other patient-related risk factors include serum creatinine level being higher than normal, glomerular filtration rate being <60 mL/min and this being caused especially by diabetic nephropathy, dehydration, congestive cardiac failure, gout, being over 70 years old and concurrent use of nephrotoxic medications (especially non-steroidal anti-

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inflammatory medications, angiotensin converting enzyme inhibitors, aminoglycosides, loop diuretics, mannitol, metformin). Patient-related risk factors also include diabetes mellitus, hypertension, low hematocrit level, hypotension, multiple myeloma, percutaneous coronary interventions, and left ventricle ejection fraction being <40%[5]. The risk of development of contrast-induced nephropathy can be assessed beforehand by Mehran risk score.

Cardiovascular parameters such as blood pressure, heart rate and coronary tonus change throughout the day due to circadian rhythm[6]. The ambulatory blood pressure measurement data for normal individuals indicates that the blood pressure is at the highest level in the morning hours, tends to decrease throughout the day and is at the lowest level at night[7]. According to this classification based on ambulatory blood pressure, the mean blood pressure during night being more than 10% lower than the mean daytime value is called dipper hypertension, and no change or less than 10% change is called non-dipper hypertension.

It is known that there is direct proportion between blood pressure level, and the grade of endothelial dysfunction, vascular damage and end-organ damage[8]. Individuals with non–dipper blood pressure have been found to have more frequent end-organ damage (ventricular hypertrophy, microalbuminuria, decreased arterial compliance, etc.), and cardiovascular morbidity and mortality[8,9]. In the present study, we investigated whether non-dipper hypertension at admission is an independent risk factor for the development of CIN in patients with CAD treated PCI.

SUBJECTS AND METHODS

Study population

This study prospectively included a total of 161 patients (108 patients with dipper, 53 with non-dipper) after the exclusion criteria were applied. All patients were informed about the study objective and gave informed written consent. Local ethics committee decision was taken before starting the study (2013/326). Patients with CAD who had normal coronary angiography plans and arterial blood pressure with or without medication were included in the study. CAD diagnosis was made based on international criteria. Patients below the age of 18 and above the age of 85, with the history of acute and/or chronic renal failure, chronic and acute hepatic failure, malignancy, previous CAD, with resistant hypertension, and with cardiogenic shock were excluded from the study. Moreover, standard medical treatment (beta-blocker, angiotensin converting enzyme inhibitor, ASA, clopidogrel and statin) was initiated for all patients based on their hemodynamic status.

Laboratory assessments

At the time of admittance, tripotassium-ethylenediaminetetraacetic acid based complete blood count, and from the blood samples taken into Isotherm-Gel Clot Activator based biochemistry tubes, biochemistry parameters (fasting blood glucose, renal function tests, liver functions tests, total lipid profile), sedimentation and complete blood count were studied for all patients. To assess the inflammatory status of the participants, C-reactive protein level was measured using BN2 nephelometer (Dade Behring, Schwalbach, Germany).

Coronary angiography

Selective coronary angiography was taken in all patients from femoral approach using standard Judkins technique. Coronary angiography analyses were performed by specialist cardiologists. The patients were evaluated to have normal coronary arteries if they had no angiographic plaque formation in all epicardial coronary arteries (including sub-branches), no irregular margins, no ectasia and no slow flow, to have CAD if they had at least one of the conditions mentioned above. Patients diagnosed with CAD were considered to have obstructive CAD if they had ≥50% stenosis in at least one coronary artery. Patients who had <50% stenosis in at least one coronary artery were considered to have non-obstructive CAD.

Ambulatory blood pressure measurement

Blood pressure measurements in the clinic were performed using sphygmomanometer according to European Society of Hypertension guidelines. Ambulatory blood pressure measurement was performed using MicrolifeWatchBP device in the 24-hour period after the patient was included based on inclusion criteria using a cuff proper for the patient's arm diameter. Blood pressure (BP) measurements were taken every 30 minutes during daytime (between 07:00 and 22:00) and every 60 minutes during night (22:00-07:00). Night, daytime and 24-hour BP measurements obtained from the measurements made for 24 hours were analyzed. The percentage of nighttime BP decrease was calculated using "Night BP decrease (%) = (Daytime BP – Night KB) x 100 / Night BP" formula. If the mean BP measured during night is less than 10% lower than the mean daytime measurement, these individuals were considered to be "non-dipper", and if the difference is 10% or more, to be "dipper". This procedure was performed at the patient's first admittance and on day 3, the groups were formed based on the average of both measurements.

Table 1: Basal characteristics and hemodynamic parameters between groups

Variable	Dipper group n=108	Non-dipper group n=53	*P* value
Age	61.2±11.2	64.6±8.7	0.049
Gender (M/F)	88/20	39/14	0.408
BMI (kg/m^2)	27.3±5.1	28.2±2.5	0.537
Hemoglobin (g/dl)	14.0±1.6	13.7±1.7	0.386
Hematocrit (%)	42.3±5.2	41.8±5.9	0.431
White Blood Cell (10^3μL)	9.1±3.5	8.7±3.8	0.267
CRP	17.8±4.3	16.7±4.9	0.286
Platelets(10^3μL)	264.5±70.6	275.3±83.7	0.525
Creatinine (mg/dl)	0.8±0.2	0.8±0.1	0.931
Glucose (mg/dl)	127±13	122±18	0.366
Total cholesterol (mg/dl)	173.2±42.6	183.1±39.7	0.358
LDL (mg/dl)	114.7±31.2	121.0±28.2	0.449
HDL mg/dl)	37.7±8.2	36.0±8.3	0.563
Triglycerides (mg/dl)	155.9±71.4	165.8±77.6	0.441
Diabetes mellitus	9 (8%)	9 (16%)	0.028
Hypertension	7 (8%)	12 (22%)	0.016
Smoking	22 (40%)	17 (34%)	0.684
Hyperlipidemia	3 (5%)	4 (7%)	0.379
Heartbeat (dk)	71±10	73±10	0.427
Systolic blood pressure (mmhg)	128.3±10.6	120.7±11.9	0.295
Diastolic blood pressure (mmhg)	74.2±10.1	75.7±10.1	0.164

BMI: Body mass index; CRP: C-reactive protein; LDL: Low density lipoprotein; HDL: High density lipoprotein

Statistical analysis

The distribution normality of the variables was tested using Kolmogorov-Smirnov test. Baseline characteristics of the patients were assessed between the groups using student's t test or Mann Whitney U test for numerical variables, and Chi-square test for categorical variables. Analysis results were assessed within 95% confidence interval, and *P* being <0.05 was considered to be a statistically significant difference. Covariates of parameters that found an importance in univariate analysis were added to the multivariate analysis model. SPSS 21.0 software (Version 21, SPSS Inc, Chicago, IL, USA) was used for basic statistical analysis.

Table 2: Echocardiography findings between groups

Variable	Dipper group n=108	Non-dipper group n=53	*P* value
LVEF %	47.3±7.8	45.3±7.4	0.149
Systolic PAB (mmhg)	30.9±9.9	32.1±10.7	0.167
LVDD (cm)	4.7±0.6	4.9±0.7	0.212
LVSD (cm)	3.1±0.5	3.0±0.4	0.101
IVSD	1.0±0.2	1.1±0.2	0.631

LVEF: left ventricular ejection fraction; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; IVSD: interventricular systolic diameter

RESULTS

A total of 161 patients, 53 being in the non-dipper group (mean age 64.6±8.7 years) and 108 in the dipper group (mean age 61.2±11.2 years) were included into the study. 74% (n=39) of the non-dipper group patients and 82% (n=88) of the dipper group patients were males (*P*=0.378). Similar results were observed between the groups for smoking status, hyperlipidemia, history heart rate, systolic blood pressure and diastolic blood pressure at admittance (*P*=0.684, *P*=0.379, *P*=0.427, *P*=0.295, *P*=0.164, respectively; Table 1). Echocardiography parameters were similar in two groups (Table 2).

No significant difference was observed between the patients' biochemical and hematological parameters (hemoglobin, hematocrit, white blood cells, C-reactive protein, platelet count, creatinine, glucose and cholesterol values) (Table 1).

When the dipper and non-dipper groups were compared for the prevalence of CAD, the number of patients with multivascular involvement was 24 (46%) in the non-dipper group and 48 (45%) in the dipper group. However, no statistically significant difference was observed between the two groups (*P*=0.910).

Table 3: Mehran evaluation of groups with and without contrast nephropathy

Variable	CIN (-) group n=142	CIN (+) group n=19	*P* value
Age	60±10.8	55±9.8	0.159
Hypotension	0	0	
IABP	0	0	
Diabetes mellitus	36	10	0.028
Creatinine (mg/dl)	0.81±0.2	0.82±0.2	0.325
Hemoglobin (g/dl)	13.9±1.6	13.6±2	0.644
Contrast (cc)	101.5±29.6	115.2±32.9	0.06
Heart failure	0	0	

IABP: intra-aortic balloon pump; CIN: contrast induced nephropathy

When both groups were compared for the development of contrast-induced nephropathy, it was detected in 11 (20%) patients in the non-dipper groups and in 8 (7%) (*P*=0.016) patients in the dipper group (Table 3). Mehran risk scoring predictor of contrast nephropathy revealed a significant difference between hypertension and diabetes mellitus groups except for non-dipper hypertension (*P*: 0.016 and *P*: 0.028, respectively). The effect of non-dipper hypertension was significant in multivariant analysis among the parameters affecting contrast nephropathy (*P*: 0.023, OR: 0.99-7.984) (Table 4).

Table 4: Multivariate analysis of parameters affecting contrast nephropathy.

Covariates	HR	Multivariate Analysis 95%CI	*P*
Non-dipper HT	3.834	0.999-7.984	0.023
DM	3.772	0.991-7.989	0.025
HT	2.538	0.821-6.733	0.025

HT: hypertensions; DM: diabetes mellitus

DISCUSSION

To the best of our knowledge, this is the first study to determine the value of non-dipper hypertension in predicting CIN for patients with CAD treated with urgent PCI. In addition, in this study we found that non-dipper hypertension causes contrast-induced nephropathy independent from Mahren risk score.

CIN is an important complication in the use of iodinated contrast media, which accounts for a significant number of cases of hospital-acquired acute kidney injury. CIN is the third most common cause of acute kidney injury in patients admitted to hospital, after ischemic and drug induced injury[10]. Studies have shown a strong association between CIN and adverse clinical outcomes, including cardiovascular complications, provision of dialysis and death[11,12]. Previous studies confirmed that the incidence of CIN in patients who have no risk factor for CIN is <2%, but the incidence in patients who are at a high risk for CIN increased to 90%[3]. In our study, the incidence of CIN (11.6%) is in agreement with recent data in patients undergoing coronary PCI[13]. CIN is associated with prolonged hospitalization and increased cost. Furthermore, CIN occurs more frequently after unplanned coronary interventions and the development of CIN is a sign of poor short- and long-term mortality after PCI in CAD despite successful coronary revascularization[14-16]. Therefore, the early identification of patients at risk of CIN is crucial to guide prophylactic therapy and diminishing the incidence of CIN in high-risk patients.

Arterial blood pressure physiologically changes throughout the day. Physiologically, blood pressure at night should be more than 10% lower than the daytime blood pressure and this is called dipper activity. If the night blood pressure drops less than 10% from the daytime value, it is called non-dipper activity[17]. "Non-dipper" blood pressure is seen in approximately 25% of the hypertensive cases, and when sub-groups such as diabetics are included, the prevalence increases even more[18]. The necessity to make such classification comes from the finding that cardiovascular morbidity and mortality is different between two groups. Individuals with non–dipper blood pressure have been found to have more frequent end-organ damage (ventricular hypertrophy, microalbuminuria, decreased arterial compliance, etc.), and cardiovascular morbidity and mortality[8,9,19].

Hypertensive renal damage is defined as the renal damage which starts or accelerates due to the effect of systemic blood pressure load (systolic, mean diastolic, pulse pressure and blood pressure variability). It is known that there is direct proportion between blood pressure level and the grade of endothelial dysfunction, vascular damage and end-organ damage. Following renal hemodynamic adaptation and glomerular hydrostatic increase, glomerular capillary semi permeability gets impaired, and as a result, albuminuria which is the most important indicator of progressive renal disease is seen. Renal hemodynamic changes due to systemic pressure increase such as increased intraglomerular pressure, changes in glomerular vascular permeability and tubular albumin reabsorption insufficiency are implicated for the occurrence of microalbuminuria in hypertensive individuals. Furthermore, in their study, Garcia-Ortiz *et al*[20] reported that albumin/creatinine ratio is negatively associated with the drop in systolic and diastolic BP at night. In their study, glomerular filtration rate was only associated with diastolic decrease. Also, in their study, Hermida *et al*[21] detected a significant association between circadian model and renal damage.

Previous studies have shown that microalbuminuria is the indicator of endothelial dysfunction and end-organ damage, and in their study, Bianchi *et al* found high microalbuminuria prevalence in non-dipper[22]. We think that in addition to the endothelial dysfunction and microalbuminuria caused by non-dipper hypertension through nitric oxide (NO), the renal ischemia induced by renal vasoconstriction due to impaired equilibrium of NO which is known as endothelium-derived relaxing factor and endothelin plays the most important role in the pathogenesis of CIN[23]. In their study comparing non-dipper and dipper patient groups for endothelial dysfunction, Higashi *et al* have assessed the 24-hour urinary excretion of NO final product nitrite/nitrate and cyclic guanosine monophosphate as a marker of endothelial dysfunction. In conclusion, 24-hour urinary nitrite/nitrate and cyclic guanosine monophosphate level was found to be significantly lower in the non-dipper patient group[24]. Moreover, obtaining positive results in studies of pre-procedural medical therapy for the prevention of endothelial dysfunction caused by contrast-induced nephropathy and the fact that these therapies mostly involve anti-hypertensive agents may

be considered as another evidence that endothelial dysfunction is involved in the association between hypertension and contrast-induced nephropathy[25].

CONCLUSION

In conclusion, this study detected that non-dipper hypertension is an independent risk factor for the development of contrast-induced nephropathy, and we think that contrast-induced nephropathy can be decreased by the pre-procedural diagnosis and treatment of non-dipper hypertension.

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REFERENCES

1. Senoo T, Motohiro M, Kamihata H, Yamamoto S, Isono T, Manabe K, *et al*. Contrast-induced nephropathy in patients undergoing emergency percutaneous coronary intervention for acute coronary syndrome. Am J Cardiol 2010; 105(5):624-8.
2. Oksuz F, Yarlioglues M, Cay S, Celik IE, Mendi MA, Kurtul A, *et al.* Predictive value of gamma-glutamyl transferase levels for contrast-induced nephropathy in patients with ST-Segment elevation myocardial infarction who underwent primary percutaneous coronary intervention. Am J Cardiol 2015; 116(5):711-6.
3. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, *et al*. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 2002; 105(19):2259-64.
4. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. CMAJ 2005; 172(11):1461-71.
5. AyşegülZümrütdalKontrastMaddeNefropatisiİ çhastalıklarıDergisi 2012; 19: 23-27.
6. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood-pressure. Lancet 1978; 1(8068):795-7.
7. Seo WS, Oh HS. The circadian rhythms of blood pressure and heart rate in hypertensive subjects: dippers and non-dippers. Yonsei Med J 2002; 43(3):320-8.
8. Pierdomenico SD, Bucci A, Costantini F, Lapenna D, Cuccurullo F, Mezzetti A. Circadian blood pressure changes and myocardial ischemia in hypertensive patients with coronary artery disease. J Am Coll Cardiol 1998; 31(7):1627-34.
9. Ohkubo T, Hozawa A, Yamaguchi J, Kikuya M, Ohmori K, Michimata M, *et al.* Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasoma study. J Hypertens 2002; 20(11):2183-9.
10. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. Clin J Am Soc Nephrol 2008; 3(3):844-61.
11. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, *et al.* The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000; 36(5):1542-8.
12. James MT, Samuel SM, Manning MA, Tonelli M, Ghali WA, Faris P, *et al.* Contrast-induced acute kidney injury and risk of adverse clinical outcomes after coronary angiography: a systematic review and meta-analysis. Circ Cardiovasc Interv 2013; 6(1):37-43.
13. Tsai TT, Patel UD, Chang TI, Kennedy KF, Masoudi FA, Matheny ME, *et al*. Contemporary incidence, predictors, and outcomes of acute kidney injury in patients undergoing percutaneous coronary interventions: insights from the NCDR Cath-PCI registry. JACC Cardiovasc Interv 2014; 7(1):1-9
14. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Wiviott SD. Short-term outcomes of acute myocardial infarction in patients with acute kidney injury: a report from the national cardiovascular data registry. Circulation 2012; 125(3):497-504.
15. Kaya A, Kaya Y, Topçu S, Gunaydin ZY, Kurt M, Tanboga IH, *et al.* Neutrophil-to-lymphocyte ratio predicts contrast-induced nephropathy in patients undergoing primary percutaneous coronary intervention. Angiology 2014; 65(1):51-6.
16. McCullough PA, Stacul F, Becker CR, Adam A, Lameire N, Tumlin JA, *et al.* CIN Consensus Working Panel. Contrast-Induced Nephropathy (CIN) Consensus Working Panel: executive summary. Rev Cardiovasc Med 2006; 7(4):177-97.
17. Fujii T, Uzu T, Nishimura M, Takeji M, Kuroda S, Nakamura S, *et al.* Circadian rhythm of natriuresis is disturbed in nondipper type of essential hypertensions. Am J Kidney Dis 1999; 33(1):29-35.
18. Atasoyu ME, Ünver S, Cingözbay Y, Evrenkaya TR, Tülbek MY. Gençnormotansifvehipertansifbireyler deayaktankanbasınc ıizlemisonuçları. TürkNefrolojiDiyalizveTransplantasyonDergisi 2001; 10: 115-22
19. Verdecchia P, Schilacci G, Borgioni C, Ciucci A, Gattobigio R, Guerrieri E, *et al.* Altered circadian blood pressure profile and prognosis. Blood Press Monit 1997; 2(6):347-52.

20. García-Ortiz L, Gómez-Marcos MA, Martín-Moreiras J, Gonzalez-Elena LJ, Recio-Rodriguez JI, Castano-Sanchez Y, *et al*. Pulse pressure and nocturnal fall in blood pressure are predictors of vascular, cardiac and renal target organ damage in hypertensive patients (LOD-RISK study). Blood Press Monit 2009; 14(4):145-51.
21. Hermida RC, Calvo C, Ayala DE, Dominguez MJ, Covelo M, Fernandez JR, *et al.* Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. Hypertension 2003; 42(3):283-90.
22. Bianchi S, Bigazzi R, Baldari G, Sgherri G, Campese VM. Diurnal variations of blood pressure and microalbuminuria in essential hypertension. Am J Hypertens 1994; 7(1):23-9.
23. Rudnick MR, Berns JS, Cohen RM, Goldfarb S. Contrast media-associated nephrotoxicity. Semin Nephrol 1997; 17(1):15-26.
24. Higashi Y, Nakagawa K, Kimura M, Noma K, Hara K, Sasaki S, *et al.* Circadian variation of blood pressure and endothelial function in patients with essential hypertension: a comparison of dippers and non-dippers. J Am Coll Cardiol 2002; 40(11):2039-43.
25. Briquori C, Marenzi G. Contrast-induced nephropathy: pharmacological prophylaxis. Kidney Int Suppl 2006; (100):S30-8.

Original Article

The effect of low-flow anesthesia on emergence agitation in pediatric patients

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ABSTRACT

Objective: We aimed to investigate the effects of low-flow sevoflurane anesthesia on emergence and recovery periods in pediatric patients undergoing adenotonsillectomy.
Design: Single center, prospective, controlled pilot study
Setting: Istanbul Medeniyet University Goztepe Training and Research Hospital, Istanbul, Turkey
Subjects: Sixty children of ASA I-II aged 2-10 years who were scheduled for adenotonsillectomy between February and May in 2016
Interventions: Patients were randomly assigned to either low-flow anesthesia or high-flow anesthesia
Main outcome measures: Heart rate (HR), mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), endtidal carbon dioxide and bispectral index values (BIS) of the patients were recorded in the operating room. The time of spontaneous ventilation beginning and extubation time were recorded while emergence from anesthesia. HR, MAP, SpO_2, pain and agitation scores were also recorded in the recovery room.
Results: Hemodynamic variables at all times, BIS, time of spontaneous ventilation beginning and extubation time were not different between the groups (P>0.05). Pain and agitation scores were lower in low flow group (P<0.05). No side effects were observed in any of the patients in groups.
Conclusions: We observed the positive effects of short-term low flow anesthesia in pediatric patients on recovery in the early postoperative period.

KEY WORDS: emergence agitation, extubation, sevoflurane

INTRODUCTION

Emergence agitation (EA) in pediatric patients after general anesthesia is a common problem. The etiological factors of EA has not been explained exactly. However, some proposed that contributors to EA are volatile anesthetics, type of surgery, patient's age, parenteral anxiety, patient anxiety, pre-existing behavior, patient and parent interaction with health-care providers[1]. EA was more common in anesthesia using sevoflurane compared to other anesthetic agents[2].

Low flow anesthesia was first described by Foldes in 1952 with a fresh gas flow of 1.0 L/min, and shown to be a reliable anesthetic technique in subsequent studies[3,4]. Low flow anesthesia is preferred to high-flow anesthesia because of its ecological and economic advantages; it also has beneficial effects for patients[5]. Low flow anesthesia has also been performed successfully in pediatric patients which was reported to be safe, cheap and advantageous[6-8].

Sevoflurane is a widely used and reliable anesthetic agent in low flow anesthesia in pediatric patients[9]. Studies on pediatric patients have shown that sevoflurane in a circle system with a fresh gas flow of 1 L/min is safe[10]. However, no study about EA after low flow sevoflurane anesthesia in adenotonsillectomy operations has been performed. In this prospective controlled study, we aimed to investigate the effect of low flow sevoflurane anesthesia on recovery period, including EA in pediatric patients undergoing adenotonsillectomy operations.

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SUBJECTS AND METHODS

This study was approved by Istanbul Medeniyet University Goztepe Training and Research Hospital Clinical Research Ethical Committee; 08.03.20016, 2016/0040. Sixty ASA I-II pediatric patients aged between 2 to 10 years who were scheduled to undergo adenotonsillectomy surgery under general anesthesia were included in the study after obtaining written informed consent from the parents. Patients with neurological or heart disease, uncontrollable asthma, acute illness or mental retardation were not included in the study. The children received midazolam 0.1 mg/kg i.v. (Demizolam, Deva Holding, Istanbul, Turkey) for premedication before administration to operating room. Children were randomly assigned into two groups as low flow (group LF, n=30) or high flow (group HF, n=30) using the computer system. Standard monitoring (electrocardiography, peripheral oxygen saturation (SpO_2), blood pressure and bispectral index values (BIS)) were performed on all patients. DatexOhmedaAvance S/5 (Newyork, NY, USA) was used as the anesthesia device, and controlled mandatory ventilation mode was preferred for ventilation. In each case, the device was tested and soda lime was checked. The inspired fraction of oxygen (FiO_2) alarm was set to 33% minimum, and endtidal carbon dioxide ($EtCO_2$) alarm was set to 50 mmHg maximum. Propofol[11] 2-2.5 mg/kg i.v. (Propofol 1%, Fresenius Kabi, Zurich, Switzerland), fentanyl 1 μg/kg i.v. (Talinat, VEM ILAC, Istanbul, Turkey) were used for induction of anesthesia. Rocuronium 0.5 mg/kg i.v. (Esmeron, Organon, Istanbul, Turkey) was used to achieve neuromuscular block, and endotracheal intubation was performed after waiting for two minutes. Ventilation was performed with the tidal volume of 6-8 ml/kg and respiratory frequency adjusting by age. The fresh gas flow was adjusted to 4 L/min with oxygen-air mixture FiO_2 being 50%, and the concentration of sevoflurane (Abbott Laboratories, USA) was adjusted to 3.5% until obtaining 1 minimum alveolar concentration (MAC) sevoflurane concentration. At the time sevoflurane value reached to 1 MAC, the fresh gas flow was decreased to 1 L/min in the low flow group, and it is kept at 4 L/min in the high flow group. Sevoflurane concentration was adjusted to keep it at 1 MAC and BIS value of 40-60, throughout the operation. Heart rate (HR), mean arterial pressure (MAP), SpO_2 and BIS values were recorded before induction, after induction, and at 5 minute intervals during the operation. FiO_2, inspired fraction of sevoflurane, $EtCO_2$ and end tidal sevoflurane concentration values were recorded at five minutes intervals during operation. All patients received acetaminophen 20 mg/kg i.v. (Perfalgan, Bristol Myers Squibb, New York, USA) just before surgery ended. At the end of the surgery, sevoflurane was discontinued and fresh gas flow was raised to 4 L/min with 100% oxygen in both groups.

When MAC value was below 0.2, BIS value raised above 70, and tidal volume was above 6 ml/kg in spontaneous ventilation, muscle relaxation was revered with atropine 0.01 mg/kg i.v. (AtropinSulfat, Galen İlac, Istanbul, Turkey) and neostigmine 0.02 mg/kg i.v. (Neostigmin, Adeka, Samsun, Turkey), and then extubated. The time of spontaneous ventilation beginning (time from discontinuation of inhalation agent to onset of spontaneous breathing) and 'extubation time' (the time from discontinuation of inhalation agent to completion of extubation) were recorded. HR, MAP, SpO_2, Aldrete Recovery Score[12], Wong Baker Pain Scale[13], and Pediatric Anesthesia Emergence Delirium (PAED)[14] values were recorded at 5 minute intervals in the post anesthetic care unit (PACU). When the Modified Aldrete Score was over 9, the patient was discharged from the PACU. Adverse reactions including respiratory depression, shivering, laryngospasm and postoperative nausea and vomiting (PONV) were recorded when they appeared. PONV was medicated with ondansetron 0.1 mg/kg i.v. (Zofer, Adeka, Istanbul, Turkey). When SpO_2 dropped below 92%, oxygen was given via face mask. On the first day after the operation, the observer checked each patient via a phone-call for adverse effects like pain, nausea, vomiting and drowsiness.

Statistical analysis was performed using SPSS (version 20; SPSS Inc., Chicago, IL USA). Demographic data such as age, body weight, duration of anesthesia and surgery were compared using unpaired student's t-test. Categorical data expressed as a number or percentages were compared by Chi-squared analysis and Fisher's exact test. The Mann-Whitney U test was used to compare recovery times, modified Aldrete Scores, PAED scores, pain scores and postoperative adverse effects between groups. For intra group pairwise comparisons of non-normally distributed parameters, Friedman test and Wilcoxon Signed Ranks test were used. Differences at $P<0.05$ were considered to be statistically significant. We used the values from a study about EA in pediatric patients[15] to calculate the sample size with SPSS program. To obtain α=0.05 and β=%95, 16 patients were calculated for each group.

RESULTS

Demographic data of the patients were not different in both groups ($P>0.05$; Table 1). There was no statistically significant difference in HR and MAP (Figure 1) values between groups. $EtCO_2$ values were higher in low flow group at 20th minute, which was statistically significant ($P<0.001$). There was no statistically significant difference in BIS values between groups ($P>0.05$). Time of beginning of

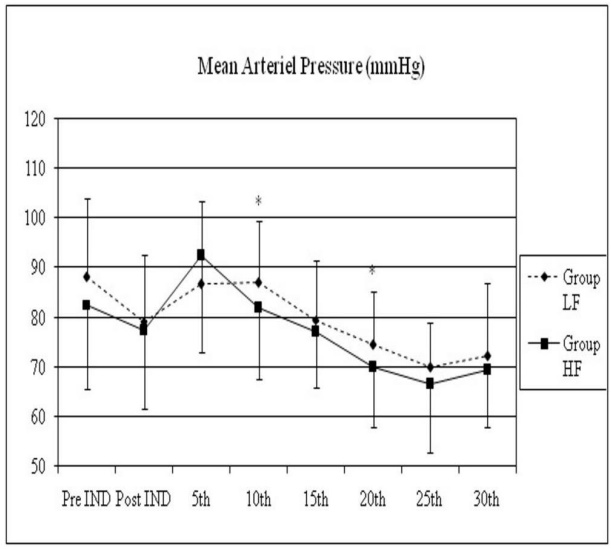

Figure 1: Intraoperative mean arterial pressure measurements.

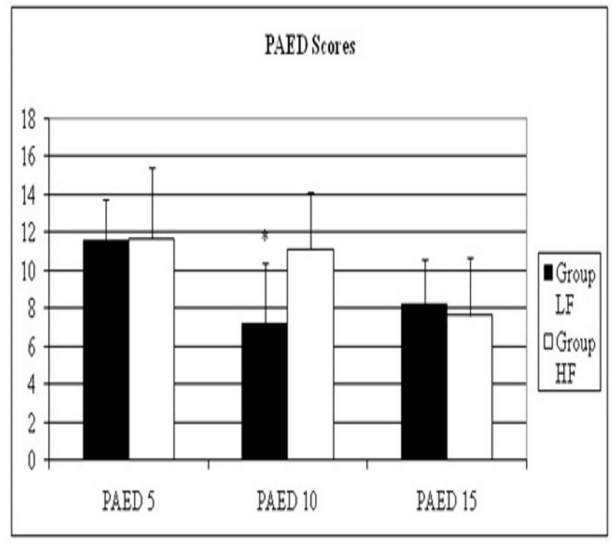

Figure 3: Pediatric Anesthesia Emergence Delirium measurements in the recovery room.

spontaneous ventilation and extubation time were similar in both groups (P>0.05). The pain scores at 5th, 10th and 15th minutes in the PACU were significantly lower in Group LF than Group HF (P<0.05; Figure 2). The PAED score at 10th minute was significantly lower in the LF group (P<0.05; Figure 3). Adverse reactions were not observed in any patient in any group.

Table 1: Demographic values in groups

Groups	Group LF	Group HF	*P*
Age (year)	5.38 (2.5-10)	6.13 (3-8)	NS
Weight (kg)	20.60 (12-29)	21.86 (13-37)	NS
Operation time (min)	35.17±7.25	36.83±9.24	NS
Time to 1 MAC (min.)	2.07±0.58	2.00±0.64	NS
Spontaneus respiration time (min.)	5.53±2.69	4.37±2.57	NS
Extubation time (min)	7.90±2.90	6.87±2.80	NS

NS: statistically non-significant values between groups; Group LF: group low flow, Group HF: group high flow; min: minute

DISCUSSION

We studied the effects of low-flow anesthesia compared with high-flow anesthesia on recovery quality in this trial, and found that the PAED score and pain scores were lower in the low-flow anesthesia group. There was no difference in beginning of spontaneous ventilation, extubation time and hemodynamic and respiratory parameters. Adverse reactions including respiratory depression, shivering, laryngospasm and PONV that were described before were not observed in any group. The mechanism responsible for EA in children remains poorly understood. A variety of explanations have been proposed. A meta-analysis of 14 randomized trials with 1100 children who underwent general anesthesia reported that EA was less likely to occur after propofol anesthesia compared with sevoflurane[16]. Some experts have attributed EA to the unique neurodevelopmental characteristics in this age group and the effects of the newer inhalational anesthetics on them[17]. Alternately, some associate EA with the unique electroencephalographic findings associated with sevoflurane anesthesia[18,19]. However, EA occurs with a similar frequency after desflurane and isoflurane, even though the electroencephalographic characteristics of these inhaled anesthetics are quite dissimilar from those of sevoflurane[20]. The mechanism for the increase in EA after sevoflurane compared with other anesthetics is unknown. In one study, no difference in the incidence of EA was noted in

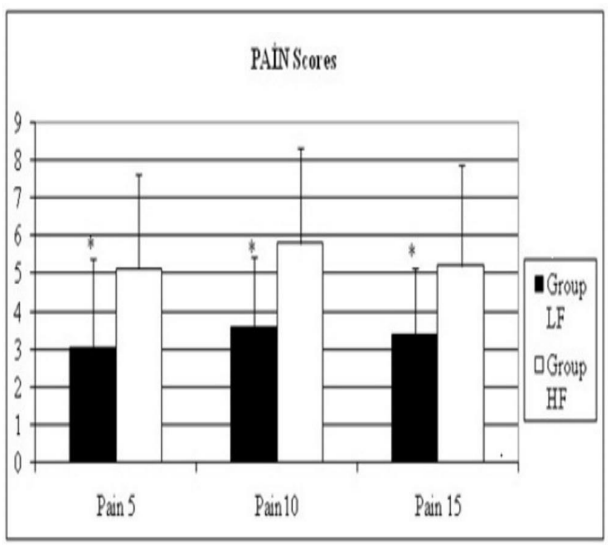

Figure 2: Wong-Baker Pain Scale measurements in the recovery room.

children randomly assigned to rapid emergence with immediate discontinuation of sevoflurane versus a controlled, gradual reduction of sevoflurane[21]. Rapid emergence from general anesthesia does not appear to be responsible from EA. In another study, there was a six-fold greater incidence of EA after sevoflurane anesthesia compared with that of propofol anesthesia (24% vs 4%), despite similar rapid emergence in both groups[22]. In our study, both the time interval between vaporizer discontinuation and spontaneous ventilation time and extubation time were similar in both groups, which may indicate that low flow anesthesia does not affect the time of emergence in this type of patients.

A number of rating scales have been developed for the diagnosis of EA to differentiate EA from postoperative pain, and to allow accurate assessment of the prevalence, predisposing factors, and prevention and treatment strategies. Currently, the PAED scale is recognized as the standard for diagnosing EA in children[23]. Two other studies found no relationship between preoperative anxiety and EA, as measured by the PAED scale[24,25]. In a small study, 32 children who underwent magnetic resonance imaging were randomized to receive general anesthesia with sevoflurane or halothane, and the incidence of EA with sevoflurane when a high diagnostic threshold was applied (similar to PAED scale) was reported to be 33%, compared with 0% with halothane[10]. The PAED score has been validated, with a score of 10 or greater yielding 64% sensitivity and 86% specificity, and a score of >12 yielding 100% sensitivity and 94.5% specificity for the diagnosis of EA[26]. In a study performed with 200 pediatric patients, the incidence of EA measured by PAED was lower in the low flow anesthesia group[27]. We also used the PAED score for evaluation of EA in our study, and PAED scores were found to be lower in patients who received low flow anesthesia, similar to previous reports.

Neither the depth of sevoflurane anesthesia[27] nor the duration of deep sevoflurane anesthesia[28] as assessed by BIS monitoring affects the incidence of EA in children. The patients were followed up with BIS monitoring in our study to maintain similar anesthesia levels in both groups, BIS scores of patients were noted at five-minute intervals, and found to be similar in both groups, which indicates that the depth of anesthesia is similar in both groups.

Low flow anesthesia is used safely in today's anesthesia practice in pediatric patients by setting alarm limits with newly developed anesthetic ventilators. Although there were statistically significant differences between the FiO_2 levels between the groups in our study, this was not likely to be clinically important because none of the measurements were lower than 50%.

Studies have focused on the prevention of EA with intravenous anesthetics by using perioperative analgesia. Children with reported agitation in the recovery room should first be assessed for potentially dangerous causes of agitation (*i.e.* hypoxia, hypotension, hypercarbia and hypoglycemia) and for pain. If the pain is a problem, they should be treated appropriately with analgesics. The pain must be controlled to make the diagnosis of EA[29]. In this study, we used paracetamol for pain management postoperatively in both groups, and the Wong-Baker pain score was used for pain assessment. In our study, the pain scores in the low-flow group were lower than those in the high-flow group at all measurement times of pain. Also, the site of surgery is important in EA. In adenotonsillectomy operations, together with the pain, irritation in the pharyngeal area may contribute to the occurrence of agitation[30]. We observed a similar finding in our study; pain and agitation scores were found to be lower in LF group. However, an explanation of how low flow affected the pain and agitation needs to be explained with new studies in this type of patients.

The MAP and HR were similar in both groups in our study. Although both of them were decreased during the operation, they did not drop lower than the normal limits. These decreases might have been due to the effect of sevoflurane on cardio respiratory reflexes, which seemed to be clinically unimportant. Adverse reactions were not detected in any patient in our study, indicating that low flow anesthesia does not increase adverse reactions in low flow sevoflurane anesthesia in children.

This study has some limitations. One limitation is the small number of participants. Although the numbers are enough to come up with strong statistical significance, it can be used as a pilot study for a larger sample sized multicenter study. As performed routinely in our clinic, we assumed that intravenous paracetamol would be enough for early postoperative period during which we measured severity of pain, which may be another limitation of the study. It could have been better if we had planned to give rescue analgesic.

CONCLUSION

We conclude that low flow anesthesia may reduce emergence delirium and postoperative pain even in short-term operations like adenotonsillectomy with no increase in the incidence of adverse events, and with no change in hemodynamic and respiratory parameters in pediatric patients.

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REFERENCES

1. Mason KP. Pediatric emergence delirium: a comprehensive review and interpretation of the literature. Br J Anaesth 2017; 118(3):335-43.
2. Cravero J, Surgenor S, Whalen K. Emergence agitation in pediatric patients after sevoflurane anesthesia and no surgery: a comparison with halothane. Pediatr Anaesth 2000; 10(4):419-24.
3. Foldes FF, Cerovolo AJ, Carpenter SL. The administration of nitrous oxide –oxygen anesthesia in closed systems. Ann Surg 1952; 136(6):978-81.
4. Baxter AD. Low and minimal flow inhalational anaesthesia. Can J Anaesth 1997; 44(6):643-53.
5. Brattwall M, Warren-Stomberg M, Hesselvik F, Jakobsson J. Brief review: theory and practice of minimal fresh gas flow anesthesia. Can J Anaesth 2012; 59(8):785-97.
6. Perkins R, Meakin GH. Economics of low-flow anaesthesia in children. Anaesthesia 1996; 51(12):1089-92.
7. Meakin GH. Low-flow anaesthesia in infants and children. Br J Anaesth 1999; 83(1):50-7.
8. Bozkurt P, Saygi Emir N, Tomatir E, Yeker Y. N_2O-free low-flow anesthesia technique for children. Acta Anaesthesiol Scand 2005; 49(9):1330-3.
9. Isik Y, Goksu S, Kocoglu H, Oner U. Low flow desflurane and sevoflurane anaesthesia in children. Eur J Anaesthesiol 2006; 23(1):60-4.
10. van der Griend BVD, Kennedy RR. Time to stop the go slow on the low flow. Paediatr Anaesth 2019; 29(4):300-1.
11. Zuckerbraun N, Pitetti RD. Rapid sequence induction. In: King C, Henretig FM (eds): Textbook of Pediatric Emergency Procedures. Baltimore: Williams & Wilkins; 2008. pp 135.
12. Aldrete JA, Kroulik DA. A postanesthetic recovery score. Anesth Analg 1970; 49(6):924-34.
13. Wong DL, Baker CM. Pain in children: comparison of assessment scales. Pediatr Nurs 1988; 14(1):9-17.
14. Sikich N, Lerman J. Development and psychometric evaluation of the pediatric anesthesia emergence delirium scale. Anesthesiology 2004; 100(5):1138-45.
15. Ryalino C, Senepathi T, Pradhana A, Yadikusumo A. Low-flow anesthesia technique reduces emergence agitation in pediatric patients underwent general anesthesia. Asian J Pharm Res 2019; 12:139-41.
16. Erdil F, Demirbilek S, Begec Z, Ozturk E, Ulger MH, Ersoy MO. The effects of dexmedetomidine and fentanyl on emergence characteristics after adenoidectomy in children. Anaesth Intensive Care 2009; 37(4):571-6.
17. Da Silva LM, Braz LG, Modolo NS. Emergence agitation in pediatric anesthesia: current features. J Pediatr (Rio J) 2008; 84(2):107-13.
18. van Hoff SL, O'Neill ES, Cohen LC, Collins BA. Does a prophylactic dose of propofol reduce emergence agitation in children receiving anesthesia? A systematic review and meta-analysis. Paediatr Anaesth 2015; 25(7):668-76.
19. Chen J, Li W, Hu X, Wang D. Emergence agitation after cataract surgery in children: a comparison of midazolam, propofol, and ketamine. Paediatr Anaesth 2010; 20(9):873-9.
20. Vlajkovic GP, Sindjelic RP. Emergence delirium in children: many questions, few answers. Anesth Analg 2007; 104(1):84-91.
21. Makkar JK, Bhatia N, Bala I, Dwivedi D, Singh PM. A comparison of single-dose dexmedetomidine with propofol for the prevention of emergence delirium after desflurane anesthesia in children. Anaesthesia 2016; 71(1):50-7.
22. Sun L, Guo R, Sun L. Dexmedetomidine for preventing sevoflurane-related emergence agitation in children: a meta-analysis of randomized controlled trials. Acta Anaesthesiol Scand 2014; 58(6):642-50.
23. Somaini M, Engelhardt T, Fumagalli R, Ingelmo PM. Emergence delirium or pain after anesthesia--how to distinguish between the two in young children: a retrospective analysis of observational studies. Br J Anaesth 2016; 116(3):377-83.
24. Berghmans JM, Poley M, Weber M, Adriaenssens P, Klein J, Himpe D, *et al.* Does the Child Behavior Checklist predict levels of preoperative anxiety at anesthetic induction and postoperative emergence delirium? A prospective cohort study. Minerva Anestesiol 2015; 81(2):145-56.
25. Joo J, Lee S, Lee Y. Emergence delirium is related to the invasiveness of strabismus surgery in preschool-age children. J Int Med Res 2014; 42(6):1311-22.
26. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. Pediatr Anesth 2010; 20(8):704-11.
27. Sato M, Shirakami G, Tazuke-Nishimura M, Matsuura S, Tanimoto K, Fukuda K. Effect of single-dose dexmedetomidine on emergence agitation and recovery profiles after sevoflurane anesthesia in pediatric ambulatory surgery. J Anesth 2010; 24(5):675-82.
28. Kain ZN, Caldwell-Andrews AA, Maranets I, McClain B, Gaal D, Mayes LC, *et al*. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg 2004; 99(6):1648-54.
29. Rosen HD, Mervitz D, Cravero JP. Pediatric emergence delirium: Canadian Pediatric Anesthesiologists' experience. Pediatr Anaesth 2016; 26(2):207-12.
30. Dahmani S, Stany I, Brasher C, Lejeune C, Bruneau B, Wood C, *et al*. Pharmacological prevention of sevoflurane- and desflurane-related emergence agitation in children: a meta-analysis of published studies. Br J Anaesth 2010; 104(2):216-23.

Original Article

Preferences, perception and impact of using dental social media in Kuwait

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ABSTRACT

Objective: To explore the pattern and impact of social media usage in the dental field as well as the users' perception on the dental accounts' existence, including their credibility level and professional image.
Design: Cross-sectional study
Setting: Online survey disseminated on social media platforms as well as to the patients attending a governmental specialized dental center in Kuwait between 24th Jan 2019 and 27th March 2019.
Subjects: Only participants aged 16 or above and using social media were eligible to participate.
Intervention: No intervention applied
Main outcome measure: The usage pattern and impact of social media platforms on oral health
Results: A total of 506 participants were included. Results showed that 76.1% of the participants (n=385) preferred to use Instagram™ among other platforms. Posting videos instead of static photos were preferred for oral health information delivery by 72% of the survey responses. The credibility level of the dental accounts varies according to the employment nature, with the governmental sector being the highest. Most of the participants (n=382, 76%) validate the dental information disseminated on social media mainly by searching on the internet (n=357, 71%), while 54% of them (n=275) found that the existence of dental accounts on social media is a major reason to find and choose a dental clinic or dentist for a visit.
Conclusions: Social media has a positive impact on oral health awareness and habits. However, educating the public about the evidence-based practice should be considered, especially with the inflated misinformation on social media.

KEY WORDS: community oral health, dental education, e-health, online health information, social media

INTRODUCTION

Social media is one of the most influential factors in our global electronic-era and has become an integral part of our daily life[1]. At least 3.5 billion people in the world are present online, which means that one in three people in the world are using social media platforms[2]. The utilization of social media in healthcare sectors is very popular worldwide and considered as a platform to provide health information, intervention, promotion and education, as well as being a communication medium between healthcare professionals, including dentists and patients[3-10]. It also has the potential to change the way we deliver care and treat some diseases and behaviors such as obesity, depression, diabetes, heart diseases and sexual behaviors[3,11].

Currently, there is a consistent trend of using web-based resources including social media as a telemedicine/teledentistry platform. Teledentistry is an evolving area that covers wide dental services such as providing remote consultations, preventive care and continuous education[12]. This trend is evident with the current severe acute respiratory syndrome coronavirus 2 pandemic, which is leading to COVID-19 disease. These resources have been used as informative platforms and a triage gate, allowing patients to be efficiently screened while avoiding the spread of virus between patients, healthcare professionals and the community[13-17].

In spite of providing beneficial opportunities on its platforms, sharing of health-related misinformation

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and inaccurate evidence on social media is found to be more prevalent and popular than accurate information[18,19]. Being actively present on social media means being aware of its usage risks including disseminating poor quality of information, damaging the professional image and violating the patient-healthcare professional boundary with its legal consequences[7]. Thus, the United Kingdom General Dental Council, American Dental Association and Australian Dental Association have published different posting protocols and guidance on using social media platforms[20-22].

This study aimed to explore the pattern and impact of social media usage in the dental field as well as the users' perception on the dental accounts' existence, including their credibility level and professional image. The reporting of the study follows the STROBE checklist[23].

SUBJECTS AND METHODS

A cross-sectional study was carried out using an online survey focusing on Kuwait's population. The survey comprised of sets of questions in Arabic regarding the use and impact of social media platforms related to dentistry. The survey was distributed electronically via social media platforms as well as to the patients attending a governmental specialized dental center in Kuwait. Participants were eligible to be enrolled into the study only if they were using any social media platform and aged 16 and above. The study was carried out from 24th Jan 2019 and 27th March 2019. Responses were entered into SPSS version 23 for statistical analyses. The study was approved by Division of Research and Surveys, Dental Administration, Ministry of Health, Kuwait, with internal number (0005/2018).

RESULTS

Demographics

A total of 506 participants were enrolled into the study; 173 (34%) male and 333 (66%) female participants. Most of the participants (n=338, 67%) were aged between 16-35 years, with university education as the highest academic level in 70% (n=356) of the participants (Table 1).

Table 1: Demographics of the participants

Variable	Frequency	Percent	Cumulative percent
Participation			
Via social media distributed hyperlink	452	89.3	89.3
Attendance at a dental clinic	54	10.7	100
Total	506	100	
Gender			
Male	173	34.2	34.2
Female	333	65.8	100
Total	506	100	
Age group			
16-25	168	33.2	33.2
26-35	170	33.6	66.8
36-45	92	18.2	85
46-55	56	11.1	96
56+	20	4	100
Total	506	100	
Nationality			
Kuwaiti	399	78.9	78.9
Non-Kuwaiti	107	21.1	100
Total	506	100	
Academic level			
Below high school	4	0.8	0.8
High school	43	8.5	9.3
University level (Bachelor/ Diploma)	356	70.4	79.6
Postgraduate	103	20.4	100
Total	506	100	

Social media usage

Instagram™ (n=385, 76%), Snapchat™ (n=226, 45%), and Twitter™ (n=175, 34.6%) were the most used social media platforms and preferred by the participants, while 9% (n=46) of participants preferred other platforms. The time spent on social media vary between participants, however, 60% (n=304) of them spent between 1 to 4 hours a day (Table 2). The data showed that 44.9% (n=227) of the participants were following five accounts or less that related to dentistry, 16.2% (n=82) following between six to ten accounts, and 11.7% (n=59) following more than ten accounts. However, 23.7% (n=120) of the participants were not following any dental related accounts and 3.6% (n=18) did not know how many dental related accounts they were following.

Post preference

Posting videos in its different forms were preferred by 72% of the responses compared to posting pictures. Similar percentages were found between the participants' preference on type of videos such as professional high-quality videos (26%), selfie videos (24%) and motion graphic videos 23% (Figure 1).

Table 2: Time consumed by the participants on social media

Time spent	Frequency	Percent	Cumulative percent
Less than 1 hour	27	5.3	5.3
Between 1 to 2 hours	149	29.4	34.8
Between 2 to 4 hours	155	30.6	65.4
More than 4 hours	133	26.3	91.7
I don't know	42	8.3	100
Total	506	100	

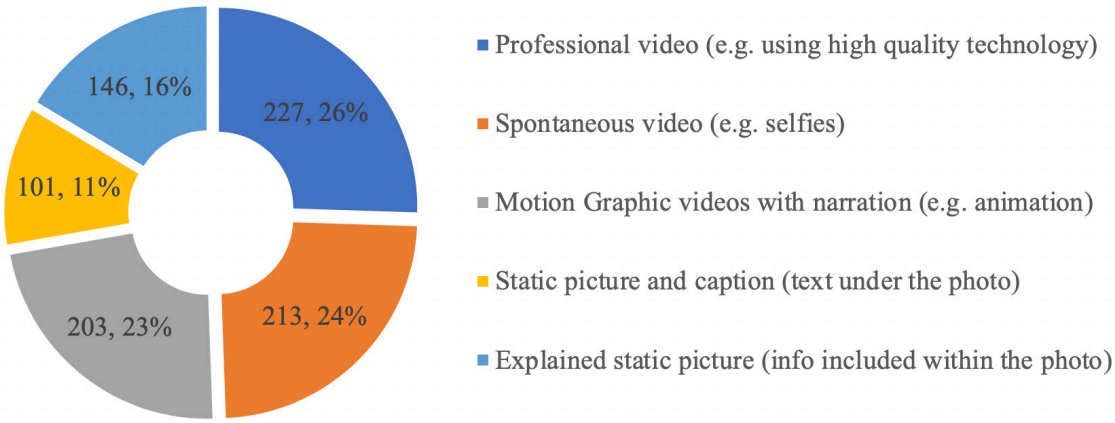

Figure 1: Type of post preferences

Impact on oral health awareness and habits

Social media usage in general has a positive impact on the participants' oral health awareness and habits; by encouraging them to visit their dentist on a regular basis (n=160, 31.6%) and correcting misconceptions and improving oral health habits (n=246, 48.6%). However, a considerable number of participants believed that dental related accounts on social media did not affect them at all (Table 3).

Psychologically speaking, data showed that 52% (n=260) and 40% (n=201) of the participants found that picture and video posts have eliminated their fears and concerns and encouraged them to visit a dentist respectively (positive impact). However, only 8.3% (n=42) and 18.8% (n=95) found that picture and video posts increased their fears and concerns and prevented them from visiting a dentist respectively (negative impact). In both type of posts, 32% of the participants in average thought that they have not been affected at all.

Online consultations and gifts

The majority of the participants (n=407, 80.4%) did not have any personal diagnostic consultation via direct messages. Similarly, 86.8% (n=439) of the participants did not receive gifts such as free file opening, dental examination or dental x-rays through social media competitions/raffles. However, of those who received gifts, only 5.9% (n=30) of them have visited the dentist.

Credibility

Credibility level has been categorized as poor credibility (no or slight credibility) and good credibility (satisfactory or high credibility). Local dentists' accounts who were working only in the governmental sector ranked with the highest level of credibility among other accounts on social media according to 78% (n=396) of the participants' perception, followed by dentists who were working in both governmental and private sectors (n=340, 67%), and dentists working only in private sector (n=261, 51%). Interestingly, non-

Table 3: The impact of using different social media platforms on oral health

Impact/Social Media Platform	Twitter		Instagram		Snapchat		General Usage	
	Frequency	%	Frequency	%	Frequency	%	Frequency	%
Encouraged me to visit a dentist on a regular basis	74	17.20	145	20.70	78	18.10	160	21.80
Corrected misconceptions and improved my oral health habits	132	30.70	237	33.80	122	28.30	246	33.50
Encouraged me to try new products and tools related to oral health	62	14.40	133	19.00	66	15.30	144	19.60
Made me take wrong personal decision related to oral health	16	3.70	23	3.30	9	2.10	33	4.50
Prompted me to undergo oral health treatment plans that I don't need in my opinion	16	3.70	34	4.90	16	3.70	34	4.60
Spent a lot of money for consultations or treatment I consider purely commercial	10	2.30	18	2.60	10	2.30	14	1.90
Didn't affect me at all	120	27.90	111	15.80	130	30.20	104	14.10
Total	430	100.0	701	100.00	431	100.00	735	100.00

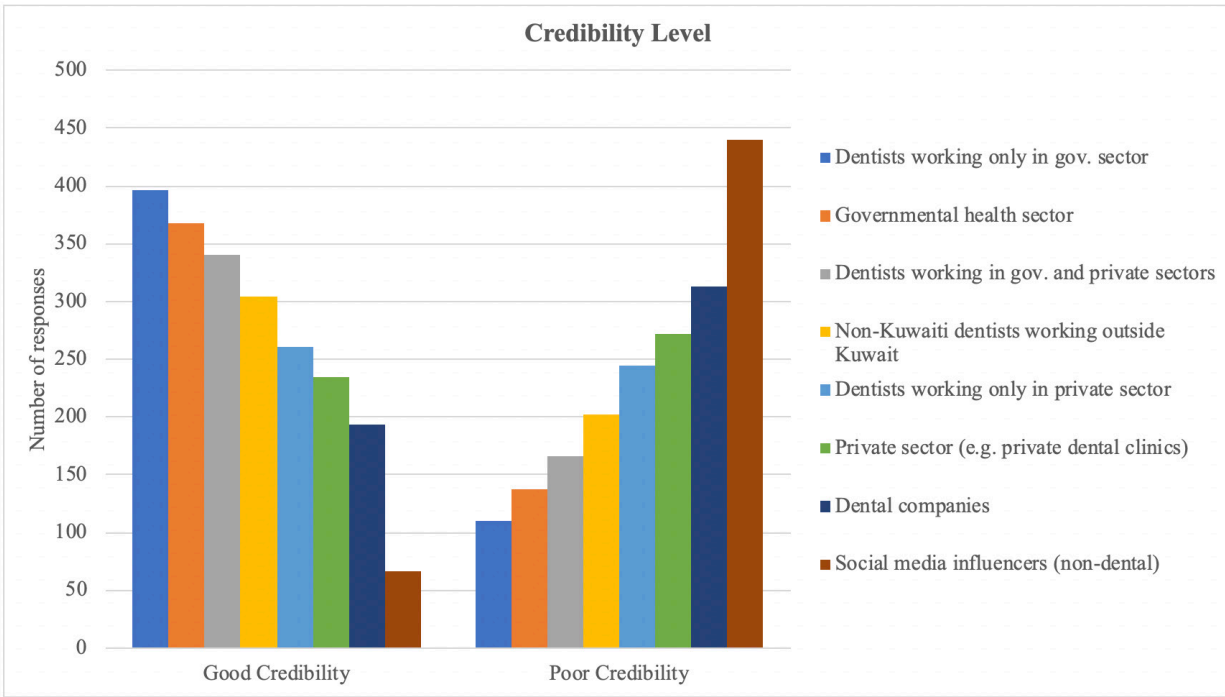

Figure 2: Comparison of the credibility level among different dental social media content accounts

Kuwaiti dentists who are working outside Kuwait have a higher credibility level (n=304, 60%) than local dentists who are working in private sectors only. In addition, official governmental dental accounts were found to be with good credibility (n=368, 73%) than the official private sectors' accounts (n=234, 46%) such as private dental clinics. On the other hand, social media influencers (non-dental) had the poorest credibility level amongst all types of accounts according to 87% (n=440) of the participants, followed by the dental companies and official private sector accounts in 62% (n=313) and 54% (n=272) respectively. Figure 2 illustrates the credibility levels among different dental social media accounts.

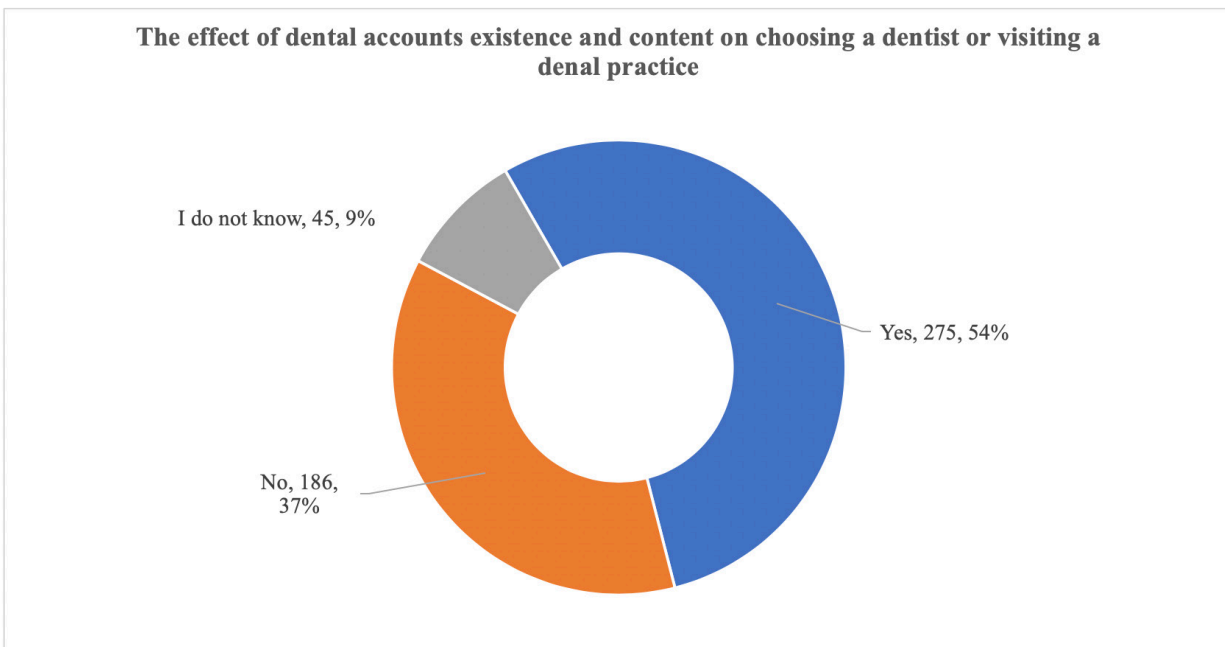

Figure 3: The response of the participants on whether dental accounts existence and content would affect their choice for a dentist or dental practice

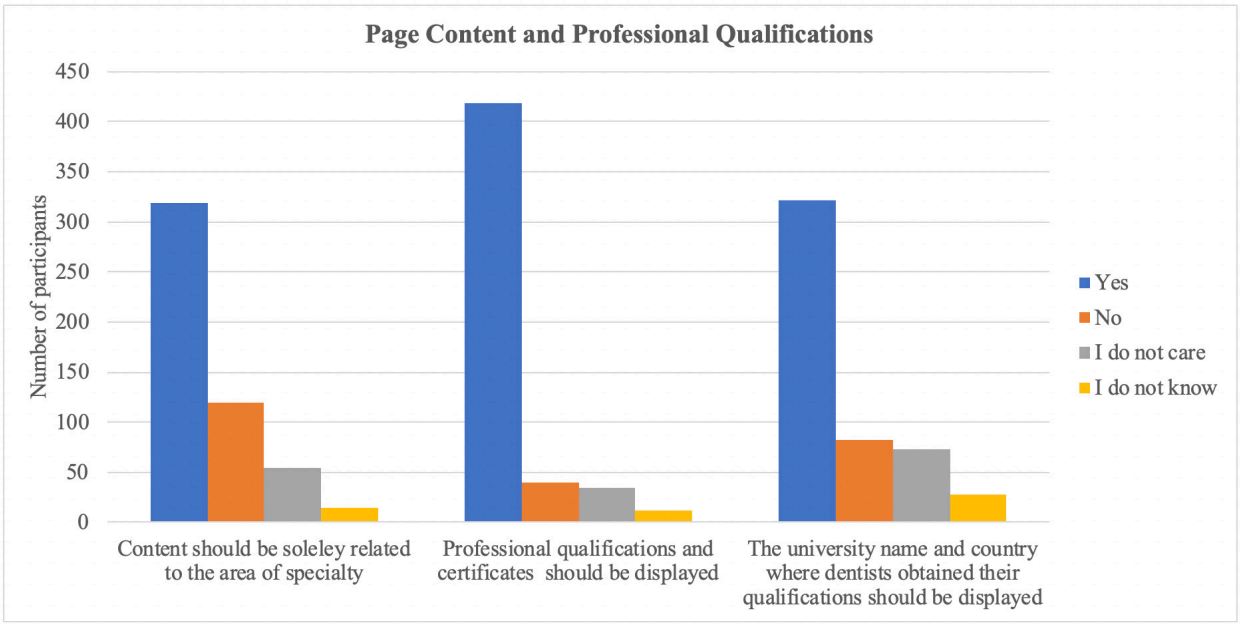

Figure 4: Participant's responses about dental accounts content and displaying professional qualification when choosing a dentist for a visit or consultation

Validity

About 10% (n=52) of the participants never validate dental advice and dental products shared on social media; however, about 14% (n=73) of them rarely validate this information. The majority of the participants (n=382, 76%) sometimes/always validate any dental advice or products posted on social media. The methods of validating the information posted on social media were mostly through searching on the internet (n=357, 71%), asking the dentist in person (n=270, 53%), asking relatives and friends based on their personal experience (n=98, 19%), and other methods (n=12, 2%).

Professional image on social media

About 54% (n=275) of the participants found that the existence of dental accounts on social media platforms including their contents was considered a major reason to find and choose a dental clinic or dentist for a visit (Figure 3). Surprisingly, 63% (n=319) of the participants preferred to see the dentists' accounts to be solely related to the area of specialty only without any personal-life involvement. In addition, 83% (n=419) of participants thought that dentists should display their qualifications on their social media pages while 64% (n=322) of them found that displaying the university name and country where dentists obtained their qualification is necessary and could be a reason for their dental visit choice. Figure 4 compares the participants' perception on the dentists' professional image on the social media.

DISCUSSION

The popularity of using social media in the dental field is currently evident, especially with the evolving features of social media platforms. The data obtained from this study showed that getting dental personnel involved in social media is vital due to its good impact on oral health. It is important to state that this study included a potential young participants group (16-year-old group), which may affect the validity of the outcomes due to their views and judgments on dental information presented on social media platforms.

Although Instagram was found to be the most used and preferred platform in Kuwait based on this study, preferences and popularity of social media platforms vary between different regions and countries[24-29]. Using these findings could help the dental account holders in focusing on the targeted population to maximize their beneficial influence on the popular social media platforms in their region of interest. Despite the high number of dental accounts present on social media, nearly 50% of the participants in this study were following only 5 or less and 23.7% of them were not following these accounts at all. This may reflect the lack of interest, poor marketing strategies or unattractive content of the dental accounts on social media. In contrast, this may show that following fewer dental accounts would be adequate instead of filling up the users' timelines with dental content. Dental account holders may think to invest in their pages in social media by posting videos and using high-tech quality

in particular if possible, as we found that 72% of the participants preferred watching videos regardless of its form in comparison to static pictures. It is pleasing to see almost 75% of the participants found that using social media in general has a positive impact on their oral health awareness and behaviors, similar to a survey that showed 67.1% of respondents believed that they changed some of the oral health behaviors based on social media information[26]. Despite the small negative psychological impact revealed in this study, having a caution message or alert at the beginning of the videos and pictures should be considered, especially in surgical-related posts.

The demand for online consultations and advice through social media is evident through comments, tweets and direct messages. However, healthcare providers on social media keep posting about the importance of having face-to-face consultations to be capable of performing physical examinations and tests for proper diagnoses. A study conducted in Dublin showed that web-based consultation with a dentist appealed to 37% of patients surveyed[10]. The author concluded that such online services seem to be unusual, if not potentially dangerous, due to the importance of taking history and preforming examination prior to drawing any conclusions regarding the patient care. At the same time, 90% of the healthcare providers who are performing online consultations found the task often or very often challenging[30]. Dentists therefore should bear in mind that providing personal online diagnostic consultations without proper history taking, examination and special tests if needed, may be considered as negligence, and thus should be avoided.

In contrast, for example with the recent COVID-19 disease pandemic, the trend was to avoid face-to-face visits temporarily in both medical and dental fields as much as possible. Healthcare providers were encouraged to offer online consultations through their official hospital applications or social media platforms as well as their social media professional accounts, mainly via direct messages. Creating virtual clinics on web-based resources which can be run from home by most senior staff has been emphasized in order to avoid physical contact with patients with unknown COVID-19 status for oral and dental problems[15]. Therefore, online-based consultation is crucial in such critical status to minimize the exposure risk for both patients and healthcare providers.

Seeking dental information on social media places a high responsibility for dental account holders to share and disseminate accurate information[11]. In spite of this great opportunity to enrich the internet including social media platforms with cutting edge health-related information, it is also a low-cost environment that keeps misinformation and fake news flourishing[18]. Dentists should carefully utilize this tool by avoiding any misinformation or giving advice based on poor quality of evidence, in which online dentists' credibility may play a major role, although that credibility is based on reader perception rather than information accuracy[31]. The variation on credibility levels observed in this study among dental personnel on social media was not surprising. Although the reasons behind this finding was not assessed in the survey, we believe that Christensen's arguments on potential negative influences on the public perception of dentists may still be valid[32]. These include having a commercial and self-promotional orientation, carrying out excessive elective treatments, or applying unjustified high fees charges. However, people are trusting dentists as they believe that dentists have the competency to protect their health and well-being, as well as recognizing their rights and dignity[33].

Validating the information or tackling potential fake news provided by dental accounts on social media is a right that everyone should be taking into consideration[34]. In this study, we found that the majority of the participants do validate the dental information disseminated on social media, however the dilemma was that 71% of them were using the internet for validation purposes. Although dentists agreed that the internet was a useful source of information on oral health, the majority of them also agreed that patients were likely to misinterpret such information, and some believed that information gained from the internet had led to patients demanding more complex treatment or inappropriate care[35]. Also, the readability and quality of websites regarding dental topics and treatments vary. Several studies analyzed dental websites to be very difficult to read or understand and contained inaccurate information, whereas other websites were good and reliable[36-39]. Moreover, as our study was conducted in Arabic, reliable and accredited Arabic dental websites almost do not exist on the internet and most of the Arabic dental information were sought through social media platforms. Thus, lack of trusted and highly credible websites, especially in Arabic language, can be of a major downside when using the internet for validation. Hence, there is a great need for valid and credible online oral health related information websites in different languages, including Arabic[37,40]. Dentists should also educate their patients on the basics of how to assess the credibility of health-related information and guide them to the concept of evidence based practice[41].

This study found that online existence of dentists on social media was a major factor to communicate with the audience, as well as reaching out new patients, as previously shown in different studies[27,42]. Not only do the presence and content of the accounts matter, but displaying the qualifications and the universities/countries from where the dentist obtained them were also considered as necessary factors to choose the dentist for a visit. Hence, it is important to make sure that your social media presence is accurate and up to date. Moreover, 63% of the participants preferred that dentists' accounts should be solely related to their area of specialty. Thus, deciding to keep the accounts representing the professional or personal identities separate or combined while thinking of its potential consequences should be taken into consideration. It is crucial to carefully think about the digital footprint that dentists are leaving on social media, which is representing them and reflecting their personal or professional identity[43].

CONCLUSION

Understanding the social media usage pattern and preferences would be extremely beneficial to oral healthcare providers. Dentists should consider their active presence on social media to raise oral health awareness and improve dental habits and attitudes. At the same time, dentists should carefully use social media platforms as a public place and not a personal diagnostic tool. This study offers guidance for the use of social media in oral health field and could be considered as a foundation for further research.

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REFERENCES

1. Stieger S, Lewetz D. A week without using social media: Results from an ecological momentary intervention study using smartphones. Cyberpsychol Behav Soc Netw 2018; 21(10):618-24.
2. Ortiz-Ospina E. The rise of social media: Our World in Data; 2019 (Accessed Dec 24, 2020, at https://ourworldindata.org/rise-of-social-media)
3. Coiera E. Social networks, social media, and social diseases. BMJ 2013; 346:f3007.
4. Parmar N, Dong L, Eisingerich AB. Connecting with your dentist on Facebook: Patients' and dentists' attitudes towards social media usage in dentistry. J Med Internet Res 2018; 20(6):e10109.
5. Antheunis ML, Tates K, Nieboer TE. Patients' and health professionals' use of social media in health care: motives, barriers and expectations. Patient Educ Couns 2013; 92(3):426-31.
6. Melkers J, Hicks D, Rosenblum S, Isett KR, Elliott J. Dental blogs, podcasts, and associated social media: Descriptive mapping and analysis. J Med Internet Res 2017; 19(7):e269.
7. Bhola S, Hellyer P. The risks and benefits of social media in dental foundation training. Br Dent J 2016; 221(10):609-13.
8. Moorhead SA, Hazlett DE, Harrison L, Carroll JK, Irwin A, Hoving C. A new dimension of health care: systematic review of the uses, benefits, and limitations of social media for health communication. J Med Internet Res 2013; 15(4):e85.
9. Snyman L, Visser JH. The adoption of social media and social media marketing by dentists in South Africa. SADJ 2014; 69(6):258, 260-4.
10. Ni Riordain R, McCreary C. Dental patients' use of the Internet. Br Dent J 2009; 207(12):583-6; 575.
11. El Tantawi M, Bakhurji E, Al-Ansari A, AlSubaie A, Al Subaie HA, AlAli A. Indicators of adolescents' preference to receive oral health information using social media. Acta Odontol Scand 2019; 77(3):213-8.
12. Estai M, Kanagasingam Y, Tennant M, Bunt S. A systematic review of the research evidence for the benefits of teledentistry. J Telemed Telecare 2018; 24(3):147-56.
13. Song X, Liu X, Wang C. The role of telemedicine during the COVID-19 epidemic in China-experience from Shandong province. Crit Care 2020; 24(1):178.
14. Machado RA, de Souza NL, Oliveira RM, Martelli Junior H, Bonan PRF. Social media and telemedicine for oral diagnosis and counselling in the COVID-19 era. Oral Oncol 2020; 105:104685.
15. Magennis P, Coulthard P. Guidance PPE for patients with emergency oral and dental problems of unknown COVID Status. BAOMS and BAOS; 2020.
16. Chan AKM, Nickson CP, Rudolph JW, Lee A, Joynt GM. Social media for rapid knowledge dissemination: early experience from the COVID-19 pandemic. Anaesthesia 2020; 75(12):1579-82.
17. Taheri MS, Falahati F, Radpour A, Karimi V, Sedaghat A, Karimi MA. Role of social media and telemedicine in diagnosis & management of COVID-19; An experience of the Iranian Society of Radiology. Arch Iran Med 2020; 23(4):285-6.
18. Wang Y, McKee M, Torbica A, Stuckler D. Systematic literature review on the spread of health-related misinformation on social media. Soc Sci Med 2019; 240:112552.
19. Llewellyn S. Covid-19: how to be careful with trust and expertise on social media. BMJ 2020; 368:m1160.
20. GDC. Guidance on using social media UK General Dental Council; 2016 (Accessed Dec 24, 2020, at https://www.gdc-uk.org/docs/default-source/student-faqs/guidance-on-using-social-media.pdf?sfvrsn=6ac9ebce_2)

21. AUDA. Policy Statement 6.24 – Social Media and Dentistry: Australian Dental Association; 2016 (Accessed Dec 24, 2020, at https://www.ada.org.au/Dental-Professionals/Policies/Dental-Practice/6-24-Social-Media-and-Dentistry/ADAPolicies_6-24_SocialMediaandDentistry_V1.aspx)
22. ADA. Social Media Posting Protocol: American Dental Association; 2019 (Accessed Dec 24, 2020, at https://www.ada.org/en/about-the-ada/american-dental-association-social-media/social-media-posting-protocol)
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE Initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Int J Surg 2014; 12(12):1495-9.
24. Office for National Statistics. Social Networking: The UK as a Leader in Europe 2013 (Accessed Dec 24, 2020, at https://webarchive.nationalarchives.gov.uk/20160107125855/http://www.ons.gov.uk/ons/rel/rdit2/internet-access---households-and-individuals/social-networking--the-uk-as-a-leader-in-europe/sty-social-networking-2012.html)
25. Salem F. The Arab World Online 2017: Digital Transformations and Societal Trends in the Age of the 4th Industrial Revolution. Dubai: MBR School of Government 2017; 3.
26. Althunayan A, Alsalhi R, Elmoazen R. Role of social media in dental health promotion and behavior change in Qassim Province, Saudi Arabia. International Journal of Medical and Health Research 2018; 4(2):168-9.
27. Ajwa N, Mohsen SA, Kuwail A, Osaif EA. The impact of using social media networks on dental treatment marketing in Saudi Arabia: The practitioners and patient's perspectives. J Oral Health Dent 2018; 2(401).
28. Gruzd A, Jacobson J, Mai P, Dubois E. The state of social media in Canada 2017. Ryerson University Social Media Lab; 2018.
29. Perrin A, Anderson M. Share of U.S. adults using social media, including Facebook, is mostly unchanged since 2018: Pew Research Center; 2019 (Accessed Dec 24, 2020, at https://www.pewresearch.org/fact-tank/2019/04/10/share-of-u-s-adults-using-social-media-including-facebook-is-mostly-unchanged-since-2018/)
30. Umefjord G, Malker H, Olofsson N, Hensjö L-O, Petersson G. Primary care physicians' experiences of carrying out consultations on the internet. Inform Prim Care 2004; 12(2):85-90.
31. Freeman KS, Spyridakis JH. An examination of factors that affect the credibility of online health information. Technical Communication 2004; 51(2):239-63.
32. Christensen GJ. The credibility of dentists. J Am Dent Assoc 2001; 132(8):1163-5.
33. Yamalik N. Dentist-patient relationship and quality care 2. Trust. Int Dent J 2005; 55(3):168-70.
34. da Silva MAD, Walmsley AD. Fake news and dental education. Br Dent J 2019; 226(6):397-9.
35. Chestnutt IG, Reynolds K. Perceptions of how the Internet has impacted on dentistry. Br Dent J 2006; 200(3):161-5, discussion 149.
36. Desai B, Alkandari N, Laskin DM. How accurate is information about diagnosis and management of temporomandibular disorders on dentist websites? Oral Surg Oral Med Oral Pathol Oral Radiol 2016; 122(3):306-9.
37. Arun M, Usman Q, Johal A. Orthodontic treatment modalities: a qualitative assessment of Internet information. J Orthod 2017; 44(2):82-9.
38. Leira Y, Castelo-Baz P, Perez-Sayans M, Blanco J, Lorenzo-Pouso AI. Available patient-centered Internet information on peri-implantitis. Can our patients understand it? Clin Oral Investig 2019; 23(4):1569-74.
39. Leung JY, Ni Riordain R, Porter S. Readability and quality of online information regarding dental treatment for patients with ischaemic heart disease. Br Dent J 2020; 228(8):609-14.
40. Almaiman S, Bahkali S, Alabdulatif N, Bahkaly A, Al-Surimi K, Househ M. Promoting oral health using social media platforms: Seeking Arabic Online Oral Health Related Information (OHRI). Stud Health Technol Inform 2016; 226:283-6.
41. Gary CJ. Fake news in dentistry: Misinformed consent. False and misleading information, easily accessible online, is complicating dentists' ethical and legal responsibility to provide their patients with the best possible treatment. N Y State Dent J 2017; 83(2):2-3.
42. Alalawi A, Aljuaid H, Natto ZS. The effect of social media on the choice of dental patients: A cross-sectional study in the city of Jeddah, Saudi Arabia. Patient Prefer Adherence 2019; 13:1685-92.
43. Connelly L. Digital footprint: Creating an effective online presence University of Edinburgh: Digital Education Unit; 2016 (Accessed Dec 24, 2020, at https://media.ed.ac.uk/media/Digital%20FootprintA%20Creating%20an%20Effective%20Online%20Presence/1_lj8fdhy6)

Case Report

Removal of fragmented malecot catheter and fragmented piece after percutaneous nephrolithotomy

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ABSTRACT

Today, percutaneous nephrolithotomy (PNL) is a widely accepted minimally invasive treatment method for kidney stones over 2 cm or where other treatment methods have failed. Fragmentation of Malecot percutaneous nephrostomy (PCN) catheter is a rare complication and was reported in only one case in literature. A 78-year-old female patient underwent PNL. Postoperative percutaneous removal of fragmented nephrostomy catheter piece was performed. In this case report, our aim was to present our diagnosis and treatment method for removing the piece of Malecot catheter detached during pulling after PNL. We performed percutaneous endoscopic approach that is a minimally invasive method for removing fragmented PCN catheters.

KEY WORDS: fragmented malecot catheter, kidney stone, percutaneous nephrolithotomy, percutaneous nephrostomy

INTRODUCTION

Today, percutaneous nephrolithotomy (PNL) is a widely accepted minimally invasive treatment method for kidney stones over 2 cm or where other treatment methods have failed[1-3]. Placement of percutaneous nephrostomy (PCN) catheter after PNL has become a procedure performed as a precaution for clot, debris and residual stone fragmentations from preventing urinary drainage[4].

Many catheters have been used for percutaneous drainage since 1955 when it was defined for the first time. Catheters most commonly used today can be named as Malecot catheter, pigtail nephrostomy catheter, Council type catheter, Foley catheter and Cook type nephrostomy catheter[5].

Several complications have been reported while placement PCN catheter after PNL or when it is kept on the patient for a long time[2,6]. Most common nephrostomy catheter related complications can be named as urinary infection, hemorrhage, adjacent organ injury and nephrostomy catheter stuck in kidney[4,5,7].

Fragmented pigtail nephrostomy catheter cases have been reported in literature[8]. The number of fragmanted re-entry Malecot catheter cases is two, including our case[9]. Our aim in this case presentation was to present our diagnosis and treatment method for the removal of fragmented distal piece remaining in pelvis and ureter after detaching of re-entry Malecot catheter located after PNL from the flaps in drainage place.

CASE REPORT

A 78-year-old female patient referred to our clinic with a complaint of left side pain. Multiple stones were observed middle pole and lower pole in the kidney urinary bladder (KUB) graphy, ultrasonography and computed tomography (Figure 1). Kidney function tests were normal in preoperative examinations. Urinary examination was in line with infection. Number of white cells was normal. Urinary culture was sterile after urinary infection treatment. Based on the medical history, it was learned that PNL was performed for left kidney stone six years ago. PNL was

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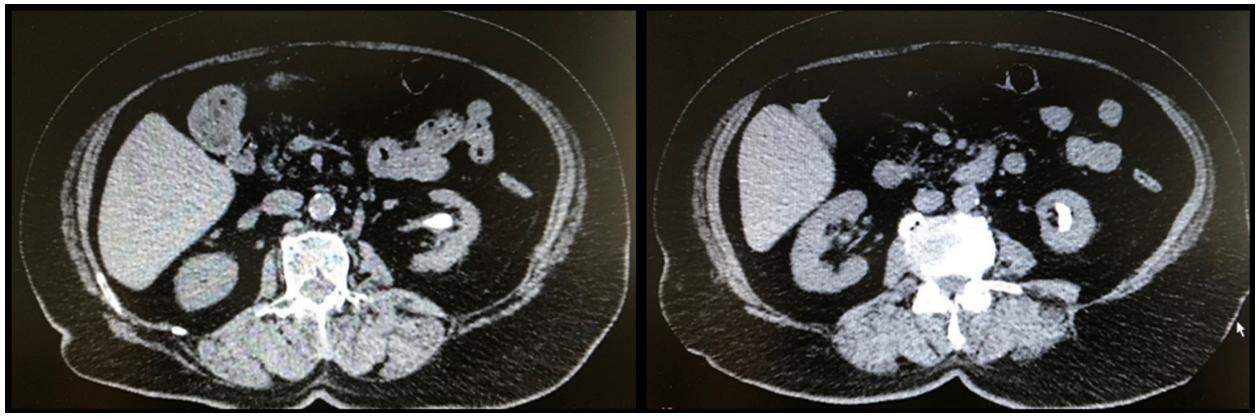

Fig 1: The appearance of middle and lower pole stones in computerized tomography

performed to the patient in the prone position under general anesthesia. Perioperative severe hemorrhage, perforation or hemodynamics disorder was not detected. 18F polyurethane re-entry Malecot catheter was located over guidewire at the end of the operation. Resistance and strain were felt while pulling the guidewire. Final catheter location was checked with fluoroscopy and the operation was ended. No residual stones were observed in postoperative KUB graphy. As the patient didn't have hemorrhage during follow-up, it was decided to pull nephrostomy catheter out on the second day. It was observed that the catheter pulled without applying tensile strength after installing mandren was detached from the valve at the drainage point and the distal piece was left inside (Figure 2). Percutaneous removal of fragmented nephrostomy catheter piece was planned. Under general anesthesia, nephroscope was located from old nephrostomy tract under fluoroscopy in prone position. The catheter was observed in the collecting system and was removed by holding with forceps (Figure 3). No residual piece was observed during fluoroscopy check. The operation was ended and the patient was discharged the next day. No additional problems were observed during follow-up. Consent was obtained from the patient to publish this case.

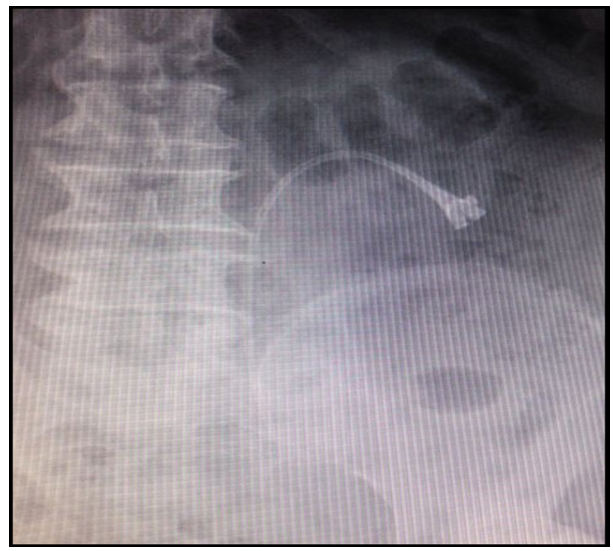

Fig 2: The KUB graphy of fragmented Re-entry Malecot nephrostomy catheter

DISCUSSION

PCN is a simple, safe and effective option for urinary drainage[8]. Most commonly used PCN catheters can be named as foley catheter (closed tip with a symmetrical balloon), cook nephrostomy catheter (open tip with

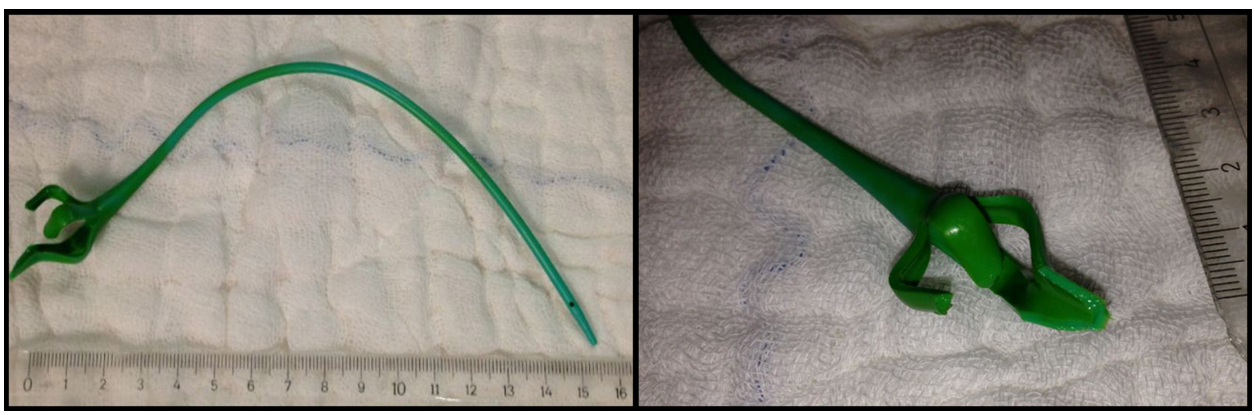

Fig 3: Fragmented parts of the re-entry Malecot nephrostomy catheter

an asymmetrical balloon), Malecot tipped catheter (fan valved) and pigtail tipped catheter[5]. PCN related complications are quite rare and generally occur due to PNL. Important PCN related complications were detected as 5% and mortality as 0.04%[8]. The most common of these can be named as urinary system infection, sepsis, hemorrhage, pneumothorax, hemothorax, intestine and adjacent organ injury, catheter encrustation, catheter dislocation and catheter fragmentation[4,7]. However, as PCN operation is applied in many cases requiring renal drainage, these complications were evaluated more among PCN rather than PNL complications[3,4,7]. We observed the complication after PNL in our case.

PCN catheters are normally resistant towards dislocation and rupture. Catheter should have adequate retention strength to prevent catheter dislocation. In a study by Canales *et al*, catheters were compared for retention strength and the weakest was detected as Malecot catheter and the strongest as Cook nephrostomy catheter[5]. In this study, it was also observed that pigtail catheter caused severe damage for renal parenchyma in case of resistance. Thus, fastening of Malecot catheters and Pigtail catheters to the skin is suggested.

Biomaterial structure, location technique, installation duration on the patient, accompanying metabolic anomalies and infection can be named among the factors effecting fragmentation[8]. El-Faqih *et al* reported that the fragmentation incidence of polyurethane catheters, which we also used in our case, was 0.3% in their study[10]. When compared to other biomaterials, it was observed that polyurethane catheters cause higher ulceration and erosion in urothelium. It was considered that this cellular damage caused encrustation on the catheter and prepared ground for fragmentation[8]. Tasca *et al* stated that polyethylene Malecot catheter valves probably caused chronic inflammation due to the pressure applied by polyethylene Malecot catheter valves on urothelium, and macrophage migration was stimulated on the area through typical foreign object reaction. It was detected that fibroblast growth factor released by macrophages caused fibrous connective tissue formation[4]. In kidney-stuck Malecot catheter cases reported in literature, it was reported that the connective tissue advancing inside the catheter valves could be the cause of sticking. In these cases, it was reported that the tissues were removed by cutting with biopsy forceps or electrocautery after entering from the side of the Malecot catheters with nephroscope or by forming tensile strength. In their cases, they cut the Malecot catheter valves with urethrotome from nephrostomy tract. Thus, many authors stated that catheter valves should be opened freely inside the renal pelvis to prevent any pressure on collective system walls[4]. Catheter valves of our patient were observed to be open and free in the control KUB graphy. They didn't even stay inside the catheter long enough to form connective tissue. There may even be a structural weakness in the catheter due to manufacturing fault.

It was reported that the duration of catheter installation on the patient plays an important role on the breakage or rupture of the catheter. In a study on 290 patients, it was detected that encrustation occurrence ratio was 9.2% in patients with catheter installation duration less than 6 weeks, 47.5% in those between 6-12 weeks and 76.3% in those over 12 weeks[10]. Catheter encrustation was not considered in our case as the installation duration was only two days.

Locating the catheter with a suitable technique is considered as an important criterion to prevent complications. Extreme torsion and stretching of the catheter during the operation may cause catheter breakage and result in its rupturing. In a study by Zisman *et al* including electron microscopic examination, it was shown that all fragmentations occurred at the level of drainage holes on the catheter and it was claimed that fragmentation would be high in these areas vulnerable to kinking[11]. Fragmenting of Malecot catheter at drainage valves in our case supports this idea. We thought that the resistance and strain we experienced while pulling the guidewire during the operation caused the over-stretching, weakening and fragmenting of the valves.

Open and endoscopic approach was preferred at case base for the removal of fragmented catheters reported in literature[8,9]. In the case presented by Ozveren *et al* in 2016, fragmented re-entry Malecot catheter was removed with open surgery and the authors evaluated this complication as a high-degree complication as it required to be operated under anesthesia, although it wasn't life-threatening according to Clavien-Dindo classification and presented this case as Clavien 3b in literature[9]. In our case, we preferred to remove the distal piece of Malecot catheter with forceps after entering the old nephrostomy tract of the patient with nephroscope.

In cases where renal drainage is required and/or after PNL operation, PCN is a frequently applied method by urologists and radiologists due to low complication ratios. Catheter should be changed at intervals in patients who require long-lasting drainage. It is not possible to decrease complications caused by the biomedical structure of the catheter. However, not using PCN after uncomplicated PNL or performing tubeless miniaturized PNL (mini PNL, super-mini PNL, ultra-mini PNL) are preferable approaches to prevent this rare complication. The most suitable technique should be selected to minimize personal complications.

CONCLUSION

The length of the removed catheter should be measured and its tips should be examined in detail while removing or changing PCN catheters. Radiological evaluation must be made after the operation and the presence of fragmentation and any residual pieces should be examined carefully. This complication which occurs rarely can be endoscopically solved easily. Percutaneous endoscopic approach is a minimally invasive method for removing fragmented PCN catheters.

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REFERENCES

1. Anderson JK, Monga M. Management of the retained percutaneous nephrostomy catheter. JSLS 2006; 10(1):126-8.
2. Seitz C, Desai M, Häcker A, Hakenberg OW, Liatsikos E, Nagele U, *et al*. Incidence, prevention, and management of complications following percutaneous nephrolitholapaxy. Eur Urol 2012; 61(1):146-58.
3. Olvera-Posada D, Tailly T, Alenezi H, Violette PD, Nott L, Denstedt JD, *et al*. Risk factors for postoperative complications of percutaneous nephrolithotomy at a tertiary referral center. J Urol 2015; 194(6):1646-51.
4. Tasca A, Cacciola A. Mini-invasive management of a rare complication of percutaneous stone treatment: entrapped nephrostomy tube. Urol Int 2004; 72(2):165-7.
5. Canales BK, Hendlin K, Braasch M, Antolak C, Reddy A, Odeh B, *et al*. Percutaneous nephrostomy catheters: drainage flow and retention strength. Urology 2005; 66(2):261-5.
6. de la Rosette J, Assimos D, Desai M, Gutierrez J, Lingeman J, Scarpa R, *et al*. The Clinical Research Office of the Endourological Society Percutaneous Nephrolithotomy Global Study: indications, complications, and outcomes in 5803 patients. J Endourol 2011; 25(1):11-7.
7. Ugras M, Gunes A, Baydinc C. Severe renal bleeding caused by a ruptured renal sheath: case report of a rare complication of percutaneous nephrolithotomy. BMC Urol 2002; 2:10.
8. Kumar S, Ganesamoni R, Nanjappa B, Sharma V. Fragmented pigtail percutaneous nephrostomy tubes: etiology and management. Korean J Urol 2012; 53(7):492-6.
9. Ozveren B, Sahin A. An unusual cause of Grade IIIb Clavien complication of percutaneous nephrolithotomy: Broken and retained Malecot nephrostomy catheter. Can Urol Assoc J 2016; 10(3-4):E122-4.
10. el-Faqih SR, Shamsuddin AB, Chakrabarti A, Atassi R, Kardar AH, Osman MK, *et al*. Polyurethane internal ureteral stents in treatment of stone patients: morbidity related to indwelling times. J Urol 1991; 146(6):1487-91.
11. Zisman A, Siegel YI, Siegmann A, Lindner A. Spontaneous ureteral stent fragmentation. J Urol 1995; 153(3 Pt 1):718-21.

Case Report

Dengue vigilance in COVID-19 pandemic

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ABSTRACT

Dengue fever is a significant health burden in Malaysia. Up to 3.6 billion people are living in the tropics and subtropical areas where dengue infection is endemic. COVID-19 is an emerging global pandemic. Dengue and COVID-19 share certain similar clinical symptoms. COVID-19 was reported to cause false positivity in dengue serology. Herein, we report two cases. The first case was a dengue and COVID-19 co-infection. The second case was a false positive dengue serology, echoing previous reported finding of false positive dengue serology by this new virus. Approach in handling dengue-like illness during this COVID-19 pandemic is discussed. Similarities and differences of these two viral diseases are summarized and discussed.

KEY WORDS: COVID-19, cytokine release syndrome, dengue, hydroxychloroquine

INTRODUCTION

Dengue fever is a mosquito-borne viral disease. It was first reported in Malaysia in 1902[1]. Beginning in 1960s, dengue began to spread into urban areas of Penang and Kuala Lumpur. By the early 1970s, it had spread to the whole of Malaysia and till date, it remains a significant health burden in Malaysia[2]. Up to 3.6 billion people are estimated to now live in the tropics and subtropical areas where dengue viruses are endemic[3]. Globally, it is estimated that approximately 50 million to 200 million dengue infections, 500,000 cases of severe dengue, and over 20,000 dengue related deaths occur annually[3].

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection occurred in Wuhan, Hubei Province, China and spread across China and beyond[4]. The World Health Organization subsequently named the disease as coronavirus disease (COVID-19)[5]. Till date, more than 2.6 million people have been infected with COVID-19, affecting more than 200 countries and territories and two international conveyances[6].

The first case of COVID-19 in Malaysia was reported on 25th January 2020. Reported new cases remained relatively low[7]. However, the trend changed in March 2020, when an upsurge of positive cases was reported, which was linked to a religious gathering held in Kuala Lumpur. Within the duration of two weeks, beginning 12th March 2020, the number of new cases exponentially increased from 149 cases to 5532 cases. At the time when this case report was written, the number of recorded deaths has gone up to 93[8]. Mortality rate in Malaysia was estimated to be 1.6%[8].

Dengue and COVID-19 may be difficult to distinguish because they share similar clinical features namely fever, muscle ache, headache, diarrhea, nausea and vomiting[9,10]. Adding to this complexity, they may share similar laboratory findings namely thrombocytopenia, leucopenia, transaminitis and acute kidney injury[9,10]. Yan *et al*[11] reported two cases where their patients initially presented with symptoms suggestive of dengue fever, demonstrated transient positive serology (IgG and IgM), which subsequently found to be positive for COVID-19. Dengue polymerase chain reaction was found to be negative. The authors highlighted the importance of considering COVID-19 when dengue rapid serology test was positive, as failure in recognition may lead to serious consequences not only to patients but also to the general public. In this case report, we illustrate

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Table 1: Summary of current reports on dengue and COVID-19

S. Notable	Age	Gender	Initial clinical presentation	Laboratory	1st Dengue serology (day of illness/ result)	2nd Dengue serology (day of illness/ result)	3rd Dengue serology	COVID-19 (Day of illness/ result)	Diagnosis	Reference
1	57y.o	Male	Fever, cough for 3 days	↓ Platelet Normal CXR ↓ lymphocyte	D3 NS1Ag/ IgM/ IgG: negative	N/A IgM/ IgG – positive	N/A Dengue PCR negative NS1Ag/ IgM/ IgG – negative	N/A Positive	False positive dengue	[11]
2	57y.o	Female	Fever, myalgia, mild cough for 4 days Diarrhea for 2 days SOB at D8	↓ Platelet ↓ lymphocyte ↑ALT/ AST/ Bilirubin CXR normal	D4 IgM positive	Dengue PCR – negative	-	D8 Positive	False positive dengue	
3	14y.o	Female	Fever, myalgia, anorexia, vomiting and headache for 4 days	↓Platelet ↓ WCC ↓ lymphocyte ↑ALT CXR normal	D4 NS1Ag/ IgG positive IgM negative	D9 IgM positive	-	D4 Positive	Dengue and COVID-19 co-infection	
4	62y.o	Male	Underlying DM/ HPT/ dyslipidemia fever, cough, myalgia and arthralgia for a week	↓ Platelet ↓ lymphocyte CXR: pneumonic patch	D7 IgG positive IgM and NS1Ag negative	D11 NS1Ag, IgM, IgG - negative	-	D7 Positive	False positive dengue	

Summary of clinical presentation, laboratory investigation, dengue laboratory investigation, COVID-19 results and final diagnosis of the cases published till date.
y.o: years old; SOB: shortness of breath; ALT: alanine transferase; AST: aspartate transferase; WCC: white cell count; CXR: chest radiograph; DM: Diabetes mellitus; HPT: hypertension; N/A: not available; NS1Ag: dengue nonstructural protein 1 antigen; IgG: immunoglobulin G, IgM: Immunoglobulin M; PCR: polymerase chain reaction; D: Day

the first reported case of COVID-19 and dengue co-infection, followed by another case which echoes Yan *et al*, highlighting the possibility of cross-reactivity of COVID-19 contributing to false positivity in dengue serology. We highlight the approach to dengue-like illness in this COVID-19 pandemic crisis. The clinical characteristic, outcome and potential treatment of these two diseases were also reviewed.

CASE REPORT

The first case was a 14-year-old female with no relevant medical illness and travelling history. She presented with fever, myalgia, anorexia, vomiting and headache for four days. She had leucopenia, thrombocytopenia and a normal chest radiograph. A rapid dengue test was performed, showing nonstructural protein 1 antigen (NS1Ag) and IgG positive. Dengue IgM was negative. A COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test was performed due to the concern of false positive in dengue serology, which surprisingly turned out to be positive. Further history revealed that she might have contracted it from her church member. Her fever resolved at day 6 of illness. She denied any worsening of chest symptoms. She was started on hydroxychloroquine (HCQ) for seven days. Thrombocytopenia resolved at day 10, preceded by resolution of the leucopenia. She experienced slight transaminitis (alanine transferase 179U/L) at recovery phase, which gradually improved when she was discharged home. A repeated dengue serology (by ELISA) at day 9 of illness demonstrated that her IgM had seroconverted to positive. The final diagnosis was dengue fever with no warning signs with COVID-19 co-infection.

The second case was a 62-year-old male with underlying comorbidity of diabetes mellitus, hypertension, dyslipidemia and stable ischemic heart

disease. He presented with fever, cough, myalgia and arthralgia for a week. Blood investigation noted thrombocytopenia with reducing trend of lymphocyte count. Dengue rapid test was performed, noted IgG positive, with negative dengue IgM and NS1Ag. In view of his respiratory symptoms and positive encounter with the religious gathering cluster mentioned above, a COVID-19 nasopharyngeal swab was taken for RT-PCR test. It was then noted to be positive. He continued to remain febrile till day 10 of illness, which he then fully resolved. Chest radiograph noted a pneumonic patch at the right middle zone; however, he did not need any oxygenation. He was treated with HCQ and lopinavir-ritonavir (Kaletra®) for 7 days. Thrombocytopenia resolved by day 8 of illness. No other end organ damage was noted. His repeated dengue serology at day 11 of illness noted negative for all NS1Ag, IgM and IgG. The first dengue rapid test was deemed to be false positive. He was discharged home well after his repeat oropharyngeal swab was negative.

DISCUSSION

In contrast to what was reported by Yan *et al*[11], we report a subject with true COVID-19 and dengue fever co-infection by demonstrating the seroconversion of IgM from negative to positive, possibly the first officially reported case worldwide. Case 2 highlights the possibility of false positive dengue rapid combo test, when only IgG was detected. A systematic approach to patients with dengue-like illness at primary care or emergency department will help to

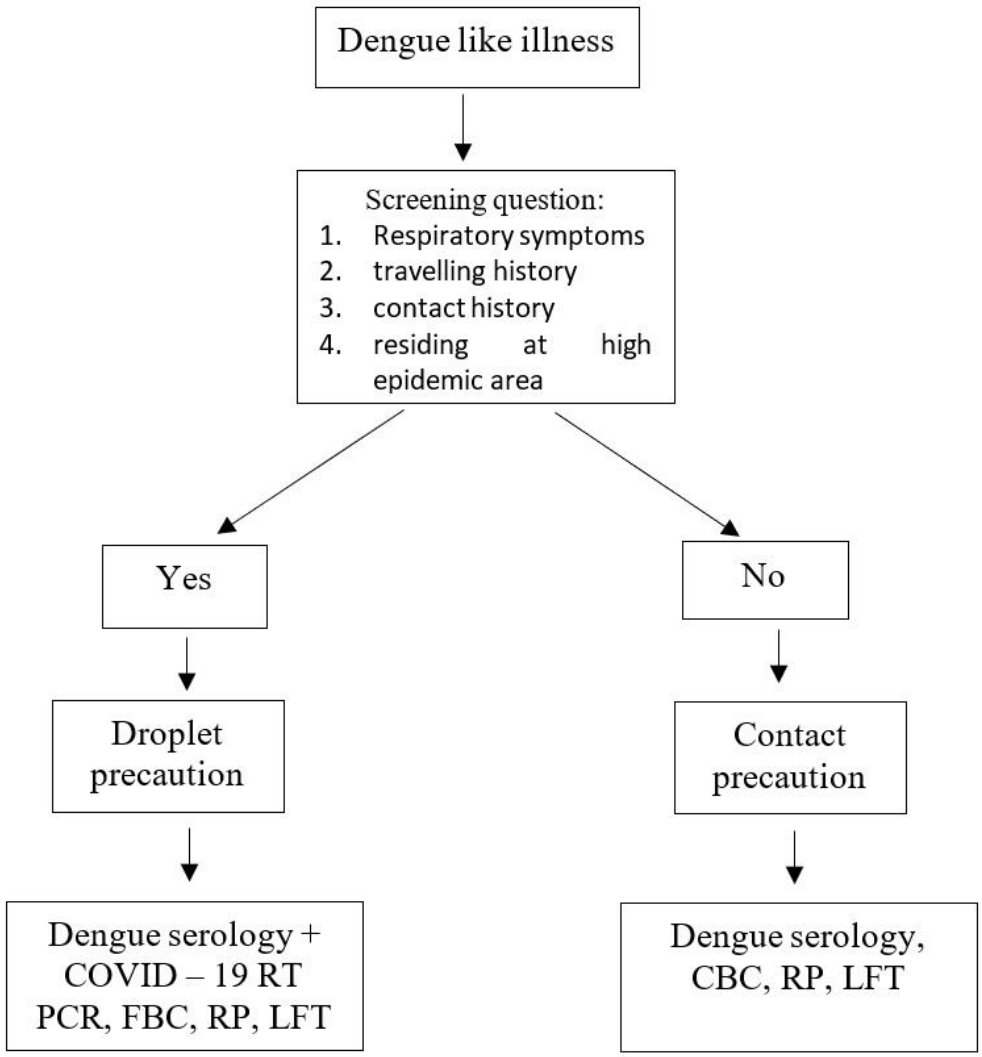

Fig 1: Proposed algorithm for approaching patients with dengue-like illness. Patients with dengue like illness, arriving at primary or emergency care settings should be screened with designated questionnaire. High risk subjects should be approached with droplet precaution, while low risk subjects should approached with contact precaution to minimize unnecessary PPE usage.
RT-PCR: reversed transcriptase polymerase chain reaction, FBC/CBC: full/ complete blood count; RP: Renal profile; LFT: Liver Function Test

Table 2: Similarities and differences of dengue and COVID-19

Variables	Dengue		COVID-19	
Clinical characteristic	Fever Headache Myalgia/bone soreness Skin rash	100% 70.89% 62.03% 54.43%	Fever Cough Myalgia or fatigue, Expectoration Dyspnea Headache or dizziness Diarrhea Nausea and vomiting	88.5% 68.6% 35.8% 28.2% 21.9% 12.1% 4.8% 3.9%
Laboratory characteristic	Leucopenia Thrombocytopenia Deranged ALT Deranged AST	75.32% 77.85% 57.59% 77.85%	Lymphocytopenia Increase of CRP Increase of LDH Leukocytopenia	64.5% 44.3% 28.3% 29.4%
Recommended diagnostic test	**< 5days** NS1Ag RT- PCR Viral culture IgM (50%)	**> 5 days** Dengue Serology	RT-PCR	
Fatality rate	1.14%		5%	
Recommended Management	Conservative fluid management		Conservative fluid management Early intubation Prone ventilation	
Potential Off-label management	Hydroxychloroquine Chloroquine IVIG Steroids		hydroxychloroquine, chloroquine, remdesivir, lopanivir-ritonavir, intravenous immunoglobulin, covalescent plasma, tocilizumab, favipiravir, traditional Chinese medicine	
References	[10,20,21]			

Clinical and laboratory characteristics, disease course, fatality rate, and management of dengue and COVID-19 were as shown.
ALT: alanine transferase; AST: aspartate transferase; CRP: C- reactive protein; LDH: lactate dehydrogenase; NS1Ag: NS1 protein antigen; RT-PCR: reverse transcriptase- polymerase chain raction; IVIG: intravenous immunoglobulin; IgM: Immunoglobulin M

safeguard the general public and health care workers in this COVID-19 pandemic. Table 1 summarizes the cases that had been published till date.

Standard precautions along with contact precautions should be advocated by wearing personal protective equipment such as apron and gloves when screening this group of patients. Subjects should be screened for respiratory symptoms, travelling history, contact history, and history of residing in a high epidemic area. Those who answer yes to any of the above questions need to be handled with droplet precautions. They should be managed in an isolation room. Appropriate personal protective equipment should be used when attending to these subjects[12]. Basic laboratory tests such as complete blood count, kidney function and liver function tests should be carried out. Dengue rapid combo test should be made available and nasopharyngeal swab or sputum should be sent for COVID-19 RT-PCR test. A N95 respirator should be worn while performing a nasopharyngeal swab. A positive dengue serology must be interpreted with care. An attempt to ascertain the diagnosis of dengue with COVID-19 co-infection or false positive serology test should be made. This step is crucial, as it will affect the monitoring and fluid management of the subject, especially in the event of a more severe disease. Figure 1 summarizes the recommended algorithm to approach patients with dengue-like symptoms.

Dengue serology can be detected using ELISA technique and is more widely used for diagnosis. It is a laboratory test of choice in later stage of disease[13,14]. IgM becomes detectable by day 3 to day 5 after onset of illness and is increasingly detectable from 50% by days 3-5 after onset of illness to 99% by day 10 of illness. Anti-dengue serum IgG is generally detectable at low titres only at the end of the first week of illness, increasing slowly thereafter. Serum IgG remains detectable after several months, and probably even for life[13,14]. Thus, a repetition of dengue serology by few days later to demonstrate the seroconversion of IgM may help in confirming the diagnosis. In the setting where dengue serology titer is presence, the increasing titer of either IgM or IgG may help to give better understanding of the diagnosis[14]. However, the interpretation of dengue serology should be taken into account that false positivity may occur due to cross-reaction with

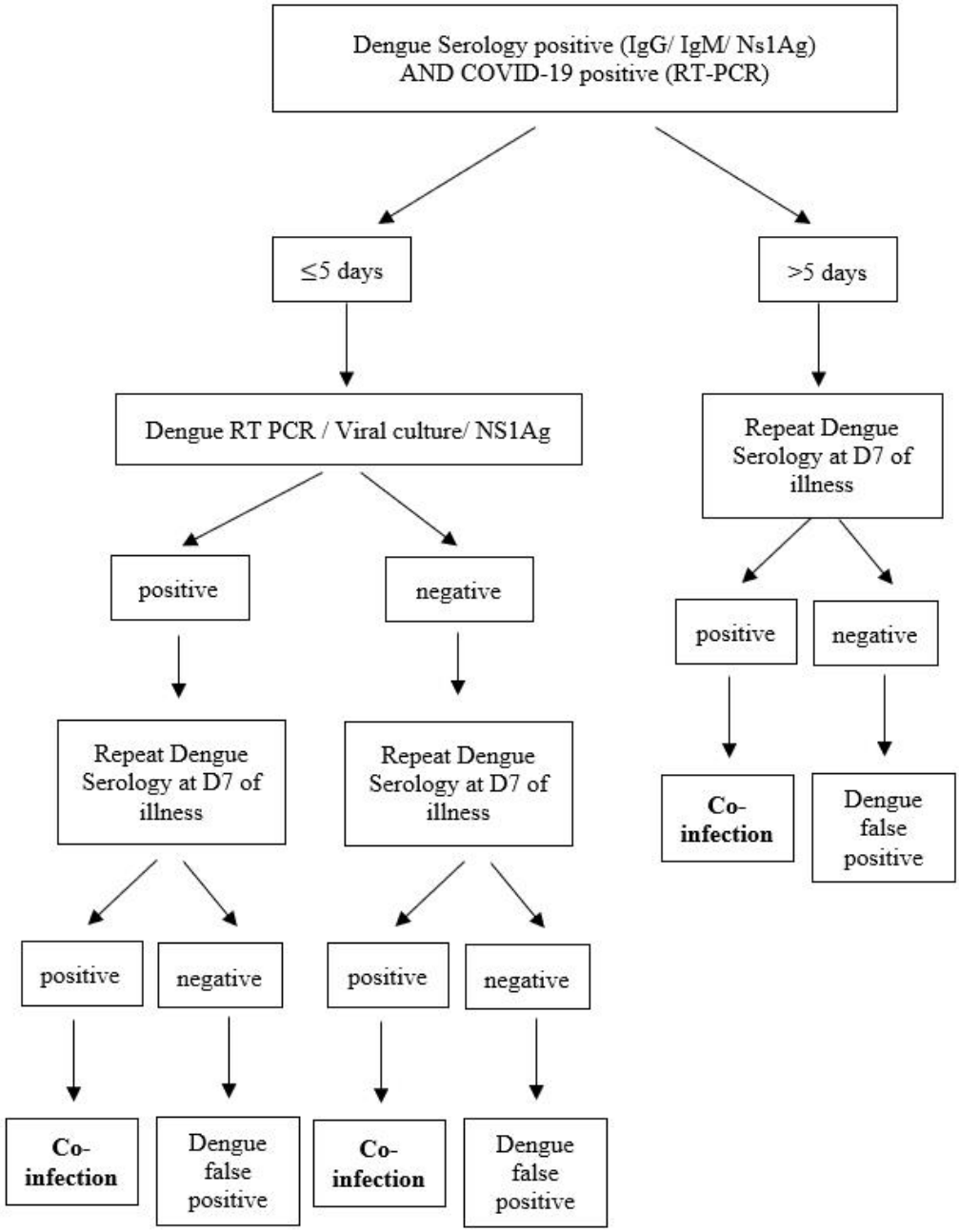

Fig 2: Proposed algorithm to ascertain dengue- COVID-19 co-infection versus dengue serology false positive
IgG/ IgM: Immunoglobulin G/ M; NS1Ag: dengue non structural protein 1 antigen; RT-PCR: reversed transcriptase polymerase chain reaction; D7: day 7

other flaviviruses (e.g. West Nile disease, Yellow Fever Virus and Japanese Encephalitis), non-flaviviruses (e.g. malaria, leptospirosis, toxoplasmosis and syphilis), and connective tissue disease (rheumatoid arthritis) [14]. During this pandemic, COVID-19 infection (as suggested in Case 2) may also cause cross-reactivity. However, more studies are required to confirm this[11].

Dengue at the early stage can be confirmed by detection of the virus, viral nucleic acid or NS1 protein antigen. NS1Ag test is easy to perform, but less sensitive than viral isolation and RNA detection. Nucleic acid detection is the most sensitive and specific method to use. Viral detection is highly specific but may not be as sensitive in detecting the virus. The latter two are highly specialized and expensive that they may not be widely available. Specimen will require special storage temperature and short transportation time between collection and extraction. The sensitivity of

all three tests mentioned are affected by the day of illness, whereby the sensitivity is reduced by day 5 of illness[13,14]. Thus, in the early stage of the disease, these tests can be considered to confirm the diagnosis of dengue. Figure 2 illustrates the proposed algorithm to approach dengue serology in the midst of COVID-19 pandemic.

Though there may be similarities in the initial clinical characteristics for both dengue and COVID-19, the clinical course, monitoring and management differ. Dengue is well known for fever of 3-7 days, followed by a critical phase (24-48 hours) and finally the recovery phase. During the critical phase, patient may have an increase in capillary permeability that leads to leakage of plasma to the extravascular space[13,14]. This will lead to hypovolemia or shock. A persistent hypoperfusion may eventually lead to organ impairment, metabolic acidosis and intravascular coagulopathy. These may ultimately lead to severe hemorrhage. Dengue warning signs include abdominal pain, persistent vomiting and/or diarrhea, restlessness, altered conscious level, clinical fluid accumulation, mucosal bleed or tender liver[13,14]. In comparison, SARS-CoV-2 virus appears to gain entrance to the lung via the angiotensin converting enzyme 2 receptors[15], thus leading to a predominant respiratory presentation and complications. Those with severe disease have a median time from disease onset to admission of 10 days, and median time to death was 16 days[16]. The presence of one or more of the following: advanced age (>60 years), cancer, more underlying diseases, or major infections appear to contribute to higher fatality[16]. Complications observed commonly includes acute respiratory distress syndrome and cardiac injury[16]. The cause of more pronounced myocardial injury may need further exploitation. However, similar to severe dengue, cytokine releasing syndrome or "cytokine storm" was observed in severe COVID-19[17-19]. This is due to an abnormal immune response involving the production of cytokines or chemokines, activation of T-lymphocytes and disturbances of haemostatic system. The mediators involved includes C3a, C5a, tumour necrosis factor-α, interleukin 2, 6 and 10, interferon-α and histamine are elevated[13]. It had been reported that the mortality rate of COVID-19 was higher (5%) than dengue (1.14%)[20,21]. The interaction of SARS-CoV-2 and dengue viruses in the host is unknown at this stage, though our first case appeared to be uncomplicated, and the disease course appeared more towards dengue infection. More case reports or prospective cohort studies are required to provide better understanding of this scenario.

The management of dengue includes close monitoring, good supportive care and judicious use of fluid replacement. Blood transfusion is advocated in approaching more severe disease, when occult hemorrhage is suspected[13,14]. Similar to severe dengue, the World Health Organization recommends conservative fluid usage during acute resuscitation in COVID-19. Crystalloid is the fluid of choice. As COVID-19 involves more severe lung disease, early intubation and prone ventilation has been advocated[22]. No medication has been listed to be effective in COVID-19. Few drugs had been repurposed and are undergoing testing. These drugs are HCQ, chloroquine (CQ), remdesivir, lopanivir-ritonavir, intravenous immunoglobulin, convalescent plasma, tocilizumab, favipiravir and traditional Chinese medicine[23]. Gautret *et al* shows that HCQ is associated with significant viral load reduction and its effect is reinforced by azithromycin[24]. It is believed that HCQ acts on the entry and post-entry stages of severe acute respiratory syndrome-associated coronavirus and SARS-CoV-2 infections, likely via effects on endosomal pH and the resulting under-glycosylation of angiotensin-converting enzyme 2 receptors that are required for viral entry[24]. The United States Food and Drug Administration issued an emergency use authorization for HCQ to be used to treat adults and adolescents who weigh 50kg or more and are hospitalized with COVID-19 for whom a clinical trial is not available or participation is not feasible[25]. However, certain experts have advised against its use in view of its potential cardiotoxicity concern, namely torsades de pointe. This is especially true when its usage is in combination with azithromycin[26]. Wang *et al* demonstrated that HCQ is able to inhibit dengue in vitro, whereby HCQ triggers the host defense machinery by inducing reactive oxidative stress and mitochondrial antiviral signal mediated innate immune activation against dengue virus infection[27]. CQ has also been reported to demonstrate dengue inhibitory ability, both in vitro[28,29] and in vivo (Aotus Monkey)[30]. CQ was found to potentially alleviate dengue related symptoms[31]. However, CQ did not demonstrate effect on duration of disease, intensity and days of fever[31]. No effect was found on viraemia and NS1 antigenemia[32]. More studies need to be done in the usage of antimalarials for COVID-19 and dengue co-infection, with more objective outcomes measured to confirm its efficacy for both diseases. Table 2 summarizes the similarities and differences between COVID-19 and dengue.

CONCLUSION

In conclusion, dengue and COVID-19 share certain clinical and laboratory characteristics. Thus, dengue like-illness needs to be approached with caution in this COVID-19 pandemic, to safeguard health care workers and public. A few medications have been repurposed

and are under investigation for COVID-19 treatment. Among those that may potentially be helpful for both COVID-19 and dengue are HCQ and CQ. However, more evidence is needed to determine its true safety and efficacy. We hope that this case report will stir more research and discussion on dengue and COVID-19 co-infection in the future, focusing on the clinical presentation, progression, laboratory findings, treatment and outcome.

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REFERENCES

1. Skae FMT. Dengue fever in Penang. Br Med J 1902; 2(2185):1581-2.
2. Gill BS. History and Epidemiology of Dengue. Denggi MyHealth Kementeri Kesihat Malaysia. 2017; Available from: http://denggi.myhealth.gov.my/history-and-epidemiology-of-dengue/?lang=en. Last accessed 23 April 2020.
3. Murray NEA, Quam MB, Wilder-Smith A. Epidemiology of dengue: Past, present and future prospects. Clin Epidemiol 2013; 5:299-309.
4. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. J Med Virol 2020; 92(4):401-2.
5. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. World Health Organization. 2020; Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virus-that-causes-it. Last accessed 23 April 2020.
6. Coronavirus Update (Live): 2,639,028 Cases and 184,263 Deaths from COVID-19 Virus Pandemic - Worldometer [Internet]. Available from: https://www.worldometers.info/coronavirus/ Last accessed: 23 April 2020.
7. Malaysia confirms first cases of coronavirus infection - Reuters [Internet]. Available from: https://www.reuters.com/article/china-health-malaysia/malaysia-confirms-first-cases-of-coronavirus-infection-idUSL4N29U03A. Last accessed: 23 April 2020.
8. COVID-19 (Maklumat Terkini) [Internet]. Available from: http://www.moh.gov.my/index.php/pages/view/2019-ncov-wuhan. Last accessed: 23 April 2020.
9. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al.* Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223):507-13.
10. Zi Y, Huang Y, Jiang P, Zheng Z, Xiong Y, Xu J, *et al.* [Analysis of clinical characteristic of 158 inpatients with dengue fever in Guangzhou area during the 2014 epidemic]. Chinese Crit Care Med 2015; 27(4):300-5. Article in Chinese.
11. Yan G, Lee CK, Lam LTM, Yan B, Chua YX, Lim AYN, *et al.* Covert COVID-19 and false-positive dengue serology in Singapore. Lancet Infect Dis 2020; 20(5):536.
12. Cook TM. Personal protective equipment during the COVID-19 pandemic - a narrative review. Anaesthesia 2020; 75(7):920-7.
13. Ministry of Health Malaysia. Clinical Practice Guidelines Management of Dengue Infection in Adults. Malaysia Heal Technol Assess Sect. 2015.
14. World Health Organization. Dengue guidelines for diagnosis, treatment, prevention and control. World Heal Organ. 2009.
15. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020; 94(7):e00127-20.
16. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, *et al.* Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368:m1091
17. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020; 395(10229):1033-4.
18. Wang WH, Lin CY, Chang K, Urbina AN, Assavalapsakul W, Thitithanyanont A, *et al*. A clinical and epidemiological survey of the largest dengue outbreak in Southern Taiwan in 2015. Int J Infect Dis 2019; 88:88-99.
19. Srikiatkhachorn A, Mathew A, Rothman AL. Immune-mediated cytokine storm and its role in severe dengue. Semin Immunopathol 2017; 39(5):563-74.
20. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, *et al.* COVID-2019 novel coronavirus patients' clinical characteristics, discharge rate and fatality rate of meta-analysis. J Med Virol 2020; 92(6):577-83.
21. Low GKK, Ogston SA, Yong MH, Gan SC, Chee HY. Global dengue death before and after the new World Health Organization 2009 case classification: A systematic review and meta-regression analysis. Acta Trop 2018; 182:237-45.

22. Alhazzani W, Møller MH, Arabi YM, Loeb M, Gong MN, Fan E, *et al.* Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020; 46(5):854-87.
23. Phua J, Weng L, Ling L, Egi M, Lim C-M, Divatia JV, *et al.* Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 2020; 8(5):506-17.
24. Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, *et al.* Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents 2020; 56(1):105949.
25. Administration D. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Hydroxychloroquine Sulfate supplied from the Stategic National Stockpile for Treatment of COVID-19 in certain hospitalized patients [Internet]. Available from: https://dailymed.nlm.nih.gov/dailymed/. Last accessed 13 April 2020.
26. Roden DM, Harrington RA, Poppas A, Russo AM. Considerations for drug interactions on QTc in exploratory COVID-19 treatment. J Am Coll Cardiol 2020; 75(20):2623-4.
27. Wang LF, Lin YS, Huang NC, Yu CY, Tsai WL, Chen JJ, *et al.* Hydroxychloroquine-inhibited dengue virus is associated with host defense machinery. J Interferon Cytokine Res 2015; 35(3):143-56.
28. Murugan K, Wei J, Alsalhi MS, Nicoletti M, Paulpandi M, Samidoss CM, *et al*. Magnetic nanoparticles are highly toxic to chloroquine-resistant Plasmodium falciparum, dengue virus (DEN-2), and their mosquito vectors. Parasitol Res 2017; 116(2):495-502.
29. Silva Farias KJ, Lima Machado PR, Lopes da Fonseca BA. Chloroquine inhibits dengue virus type 2 replication in Vero cells but not in C6/36 cells. Sci World J 2013; 2013:282734.
30. Silva Farias KJ, Machado PRL, Muniz JAPC, Imbeloni AA, Lopes da Fonseca BA. Antiviral activity of chloroquine against dengue virus type 2 replication in Aotus monkeys. Viral Immunol 2015; 28(3):161-9.
31. Borges MC, Castro LA, Lopes da Fonseca BA. Chloroquine use improves dengue-related symptoms. Mem Inst Oswaldo Cruz 2013; 108(5):596-9.
32. Tricou V, Minh NN, Van TP, Lee SJ, Farrar J, Wills B, *et al.* A randomized controlled trial of chloroquine for the treatment of dengue in Vietnamese adults. PLoS Negl Trop Dis 2010; 4(8):e785.

Case Report

An unusual reason of mediastinitis

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ABSTRACT

Descending necrotizing mediastinitis (DNM) is a rare and life threatening condition. The mortality and morbidity rate of DNM is high. Early diagnosis and aggressive surgical treatment are important. Etiology of DNM often originates from odontogenic, pharyngeal or cervical region infections. In this article, we present an unusual reason of DNM experience. A 50-year-old male who referred to our center was mistakenly diagnosed with a tumor, but he had idiopathic DNM that had no etiological cause, except eating ice. In conclusion, DNM may show tumor-like images in radiological imaging. Eating ice causes transient minimally invasive trauma to the esophagus and may cause DNM.

KEY WORDS: descending necrotizing mediastinitis, eating ice, unusual reason

INTRODUCTION

Descending necrotizing mediastinitis (DNM) is an uncommon but life threatening condition[1,2]. Due to high morbidity and mortality, early diagnosis and aggressive surgical treatment are important[3,4]. Etiology of DNM often originates from odontogenic, pharyngeal or cervical region infections[2-5]. In this article, we present an unusual reason of DNM experience.

CASE REPORT

A previously healthy 50-year-old male patient who was referred to the outer center was mistakenly diagnosed with a tumor and presented to the emergency department for high temperature and dysphagia. On admission, blood pressure was 110/70 mm Hg, respiration rate was 30 breath/min (minute), pulse rate was 120 beat/min, and his body temperature was 37.9°C. Laboratory investigations revealed leucocytosis with neutrophilia, haemoglobin rate was 13g/dl, platelets was 411000/mm^3, C-reactive protein was 308 mg/L.C and blood sugar was high. Physical examination showed dyspnea, ortopnea, cyanosed and decreased breath sounds on both sides of the chest. A mild infrahyoid soft neck swelling was noted. Computed thorax tomography (CT) observed wide mediastenal abceses of increased size compared to the outer center in the paravertebral area and extending from retrotracheal area to the right mediastenal area (Figure 1 a, b). He didn't have any compliant of toothache or oropharengial infection, his compliant started with dysphagia. The patient underwent esophagoscopy and no pathology was detected. The patient had a long history of eating ice and there was no other reason for the cause of DNM.

The patient underwent emergency surgery and mediastenal abceses were drained with posterolateral thoracotomy. Bacteriological results from samples obtained from the mediastenum revealed Staphylococcus aureus. Postoperative meropenem and teicoplanin was provided. On hospital day seven, another cervicothoracic CT was done and significant reduction was noted in cervical and mediastenal abcess size (Figure 2). After full recovery, the patient was discharged on day 15 of hospitalization and follow-up continues without problems.

DISCUSSION

DNM is a rare and life threatening condition[2]. There are studies showing that mortality rate can reach up to 40%[2]. It is defined as an inflammation that comes from the cervical or oral region, which fills interpleural spaces of mediastinal structure's connective tissue[3-5].

Young men are often affected by DNM[3-5]. Odontogenic infection (40-60%), retropharyngeal abscess (14%) and peritonsillar abscess (11%) are the

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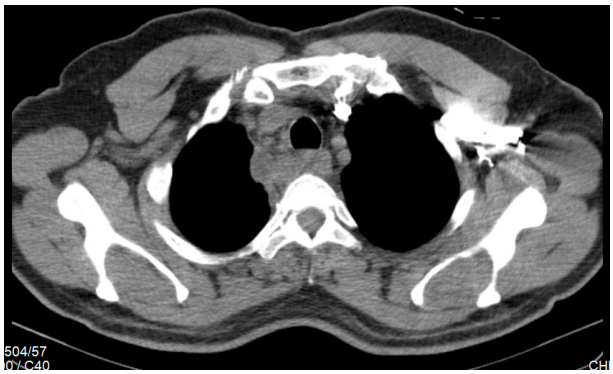

Figure 1a: Out center thorax CT

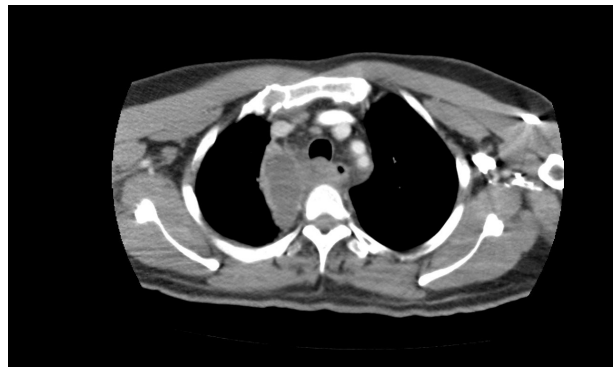

Figure 1b: Pre-operation thorax CT

more common causes of descending mediastinitis[3]. Old age, chronic illness such as diabetes, alcoholism, smoking, immunodeficiency and neoplastic illness are important predisposing factors[2-4]. In our case, a 50-year-old male who had no risk factors other than eating ice, CT scans and endoscopic imaging showed no pathological cause. We thought that eating ice could cause transient minimally invasive trauma to the esophagus and cause DNM.

There are diagnostic criteria for DNM established by Estrera *et al* and anatomical extent classification by Endo *et al*[3,5]. For DNM in our patient, there were Estrera *et al*'s first three diagnostic criteria, and was type 1 according to Endo *et al*'s classification. There are a limited number of meta-analyzes and randomized controlled trials or clinical practice guidelines on the diagnosis and treatment of DNM in the literature[3,5].

Chest pain, high fever, fatigue, tachycardia, dyspnea and non-productive cough are the main symptoms and signs in mediastinitis[3-6]. Blood tests and radiological imaging in DNM are often enough to diagnose. Our patient had no symptoms other than onset fatigue and cough but on radiological examination, there was a lesion which increased in size, suggesting DNM, and there was an increase in white blood cells and blood infection markers from blood tests.

The accepted treatment approach in DNM is early aggressive surgical treatment, appropriate antibiotherapy, follow-up with serial radiological imaging and blood tests, nutritional support and elimination of primary orgin. We performed surgical treatment (mediastinal debridement and drainage by thoracotomy) on our patient who was diagnosed as having a tumor in an external center, provided appropriate antibiotherapy, provided nutritional support and followed up with radiological and blood tests.

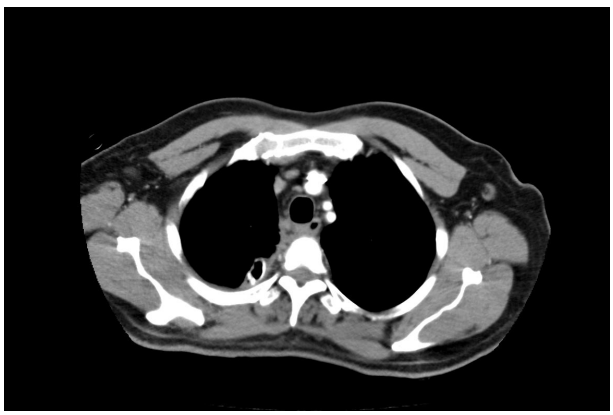

Figure 2: Seventh day thorax CT

CONCLUSION

DNM may show tumor-like images in radiological imaging and eating ice may cause transient minimally invasive trauma to the esophagus and cause DNM. Even if there is no clear cause in the etiology, early diagnosis and aggressive surgical treatment are life-saving because of the high mortality and morbidity of DNM.

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The article, including the relevant data, figures and tables, has not previously been published in a journal, and is not evaluated in another journal for simultaneous publication.

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REFERENCES

1. Van Schooneveld TC, Rupp ME. Mediastinitis, In: Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. Philadelphia: Elsevier; 2014. p 1080-1090.

2. Elsahy TG, Alotair HA, Alzeer AH, Al-Nassar SA. Descending necrotizing mediastinitis. Saudi Med J 2014; 35(9):1123-6.
3. Cirino LMI, Elias FM, de Almeida JLJ. Descending mediastinitis: a review. Sao Paulo Med J 2006; 124(5):285-90.
4. Kilic D. [Medıastenın akut ve kronik enfeksıyonları]. Toraks Cerrahisi Bulteni 2011; 2:61-65. Article in Turkish.
5. Prado-Calleros HM, Jimenez-Fuentes E, Jimenez-Escobar I. Descending necrotizing mediastinitis: Systematic review on its treatment in the last 6 years, 75 years after its description. Head Neck 2016; 38 Suppl 1:E2275-83.
6. Sezer HF. [Death due to late intervened fishbone.] Sağlık Akademisi Kastamonu 2019; 4(1):67-74. Article in Turkish.

Case Report

Gracilis muscle flaps combined with bilateral V-Y advancement gluteal flaps for reconstruction of large sacral defect after abdominoperineal resection

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ABSTRACT

Abdominoperineal resection (APR) is a first-choice treatment for anorectal cancer. Unfortunately, perineal wound complications after APR are a common problem. To decrease the incidence of postoperative wound complications, immediate reconstruction in collaboration with plastic surgeons can be performed. We present the case of a 48-year-old man with rectal cancer who underwent extended APR with vertical rectus abdominis flap reconstruction, which was complicated by flap necrosis. To manage the complication, two gracilis muscle flaps were used to reconstruct the pelvic floor and obliterate the dead space. The remaining wound was closed with bilateral V-Y advancement gluteal flaps. We achieved satisfactory results in healing a large perineal defect. Therefore, our case suggests that the application of gracilis muscle flaps combined with bilateral V-Y advancement gluteal flaps is a good option for reconstructing large perineal defects.

KEY WORDS: abdominoperineal resection complications, anorectal cancer, perineal reconstruction

INTRODUCTION

The incidence of anorectal carcinoma has markedly increased in the last decades[1]. Usually, at the time of diagnosis, the lesion has grown locally and is already at an advanced stage. Although chemoradiotherapy can provide temporary symptomatic relief, it does not affect survival. Therefore, extensive tumor resection, such as abdominoperineal resection (APR), offers the only possibility of cure and prolonged survival.

Nevertheless, extended pelvic exenterations result in large perineal defects that are challenging to repair. Various wound complications are observed in 36-65% of the patients[2]. Primary closure is not always an option because it is related to a high risk of wound dehiscence and prolonged recovery[3]. The presence of a large dead space leads to infection and abscess formation. Therefore, a wide variety of reconstruction options for the management of large perineal wounds have been proposed. Regional musculocutaneous (vertical rectus abdominis, gluteus maximus), fasciocutaneous (anterior lateral thigh, V-Y advancement), muscular (gracilis, gluteus maximus), or omental flaps can be used. In some cases, free microsurgical flaps such as thoracodorsal artery perforator or anterior lateral thigh flaps can be harvested when regional flaps are not wide enough to cover the defect or in the presence

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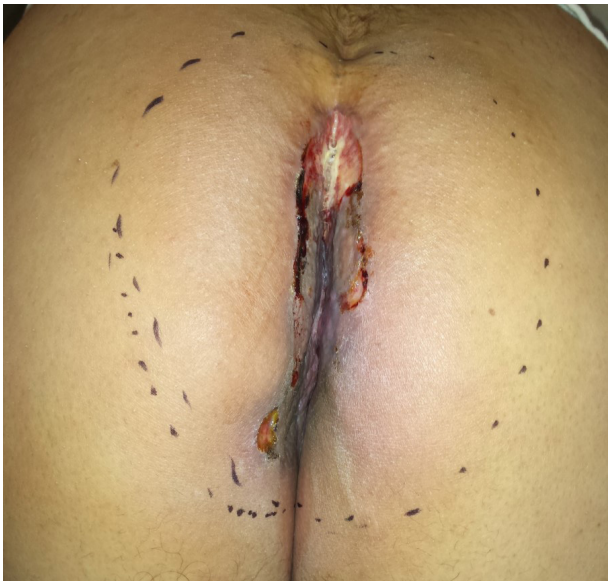

Fig 1: Preoperative view: inflammated pararectal tissue (the patient lies in prone position)

of other contraindications. All kinds of flaps can be used in combination to achieve the best outcome. Reconstruction provides a barrier to infection and reduces wound-healing complications[4].

The most universally applied flap is the vertical rectus abdominis myocutaneous (VRAM) flap[5,6]. However, no consensus exists about which reconstructive approach should be adopted after a complicated reconstruction that led to morbidities, such as vascularization issues and flap necrosis. We present a case of complicated perineal reconstruction after an extended APR, with a satisfactory outcome in the follow-up observation. The aim of this report was to discuss our surgical management in detail and to emphasize the importance of perineal reconstruction.

CASE REPORT

A 48-year-old man with complaints of pruritus and recurrent abscesses in the area of the perineum that

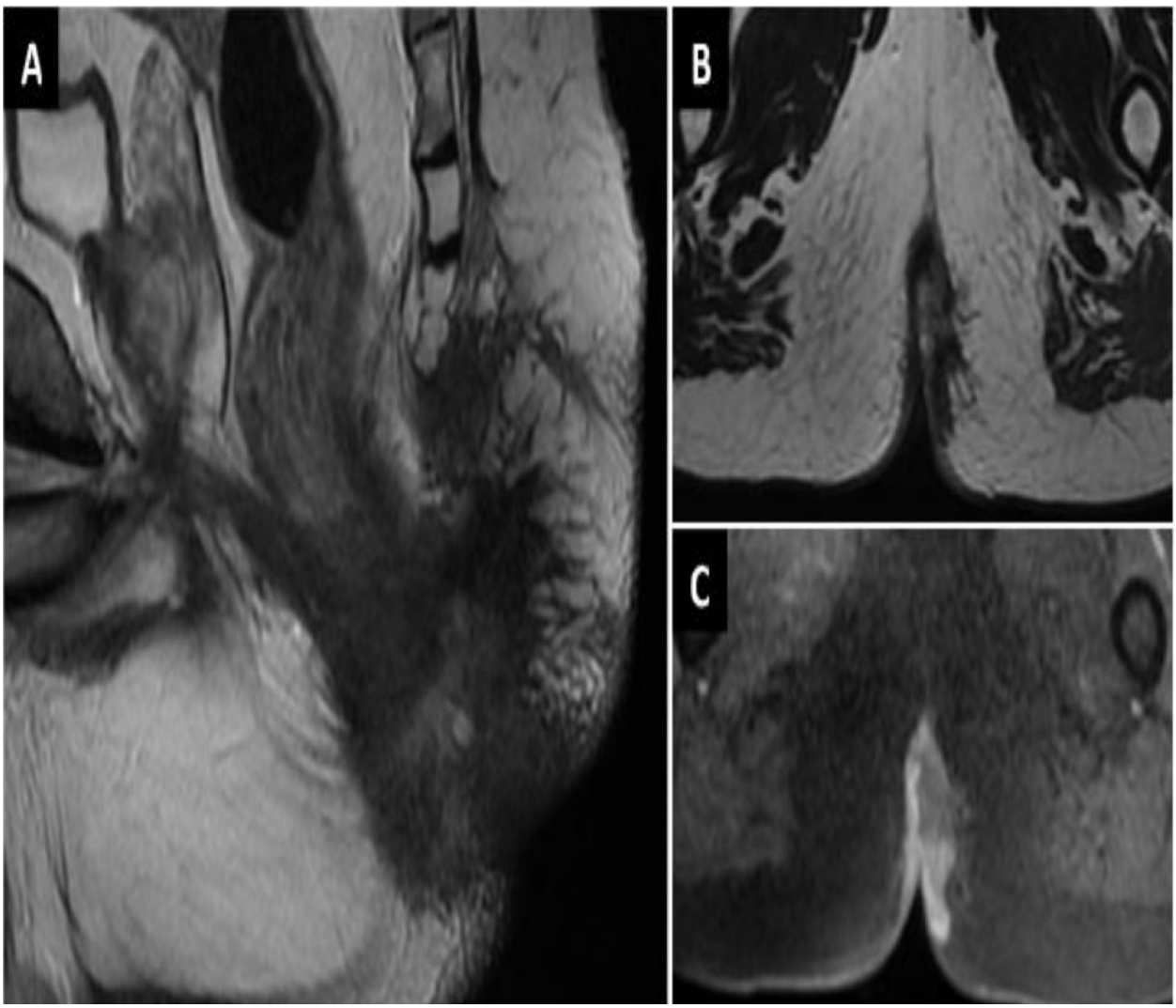

Fig 2: Local spread of anal adenocarcinoma in the distal anal canal and to the surrounding subcutaneous tissue bilaterally demonstrated on sagittal T2-weighted (A), axial T2-weighted (B) and axial T1-weighted, fat-suppressed contrast-enhanced (C) MR images.

had persisted for 10 years was investigated in Vilnius University Hospital Santaros Klinikos. The evaluation revealed inflamed, firm, cicatrized pararectal tissue including the left and right gluteal regions (Fig. 1).

Colonoscopy with biopsy and magnetic resonance imaging were performed, and well-differentiated (G1) mucinous anal adenocarcinoma was diagnosed (Fig. 2).

A multidisciplinary consultation involving radiologists, medical and surgical oncologists, and plastic surgeons led to the decision of primarily creating a colostomy, followed by radiation therapy and subsequently APR with perineal reconstruction using the VRAM flap. Six months after the colostomy surgery, the second stage of surgery was performed.

Operation technique

A 10-cm-wide and 25-cm-long skin paddle was designed above the right rectus abdominis muscle. The anterior rectus sheath was incised; the muscle was separated from its lower sheath; and the deep inferior epigastric artery and vein were mobilized as a pedicle (Fig. 3).

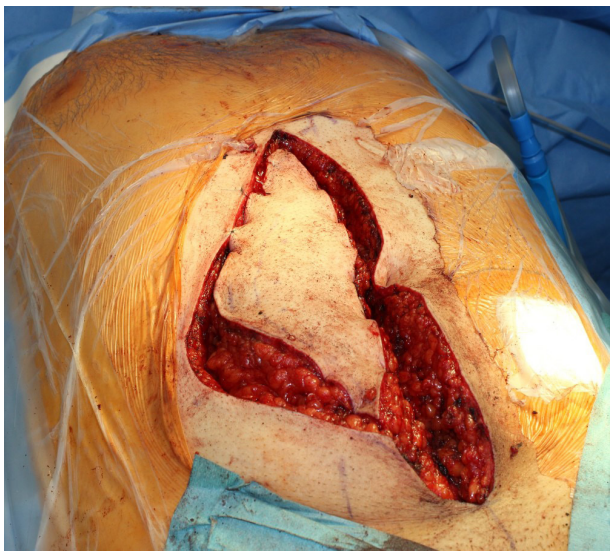

Fig 3: Visualization of perineal defect reconstruction with VRAM flap - elevated VRAM flap before laparatomy and APR (in supine position)

Thereafter, laparotomy was performed through the same incision. The mesorectum was dissected to the level of the coccyx, and complete excision of the external and internal anal sphincters and partial excision of the levator ani muscle were performed through the perineal portion. Subsequently, the rectum was removed through the perineum, leaving a 10 * 8 cm sacral defect (Fig. 4).

The rectus muscle was cranially and caudally dissected, and the VRAM flap was left only on its vessel pedicle and transposed through the tunnel into the perineal defect. The vessel pedicle appeared to be under tension, but the tunnel was too narrow to pull the flap backwards. Therefore, we decided to incise the aponeurosis and parietal peritoneum to widen the tunnel. The tension was reduced, and sluggish circulation was observed in the flap. The most proximal part of the flap was deepithelialized and used to fill the space. The flap was sutured to the perineal tissue without tension with interrupted sutures (Fig. 5). The operation time was 565 min, and the blood loss amount was 500 mL.

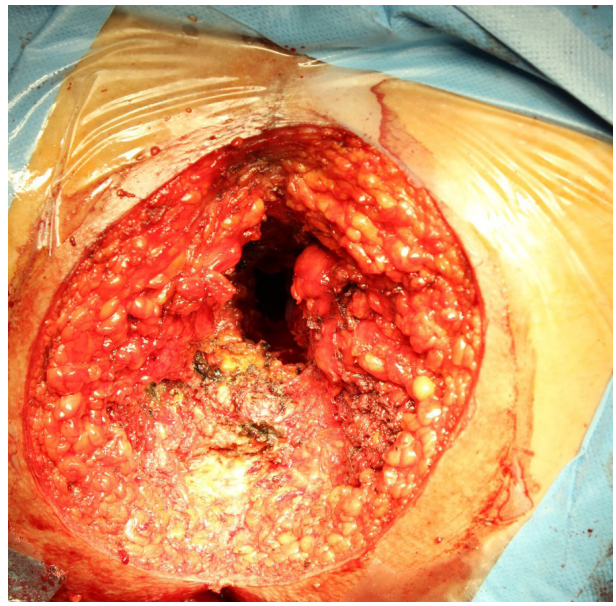

Fig 4: Large perineal defect (10 x 8 cm) after APR (in lithotomy position)

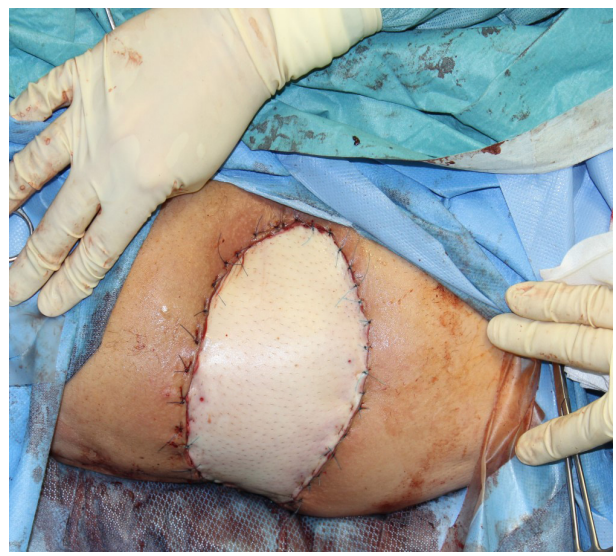

Fig 5: VRAM flap has fully covered perineal defect (in lithotomy position)

The early postoperative period was uneventful; however, 5 days later, when the patient was allowed to begin walking, the flap circulation deteriorated. A few days later, the first signs of VRAM flap necrosis became evident (Fig. 6).

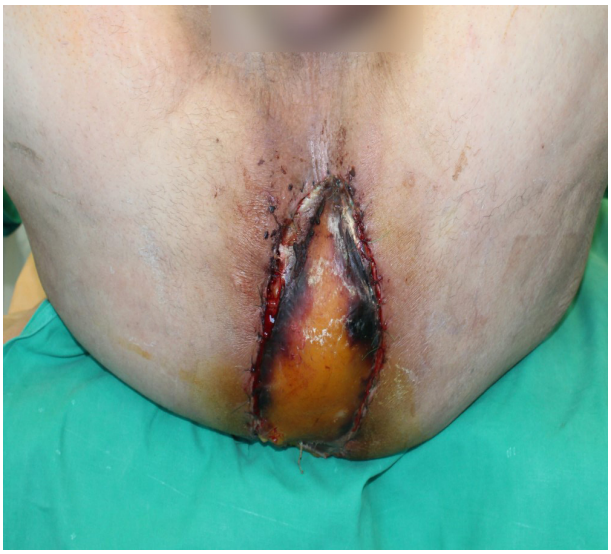

Fig 6: VRAM flap necrosis view before the second operation (the patient in lithotomy position)

Necrosis and flap loss were confirmed with computed tomography. Therefore, we decided to remove the necrotic flap and to obliterate the perineal defect, which was covered with two gracilis muscle flaps followed by bilateral V-Y advancement gluteal flaps.

Incisions were made on the medial surfaces of both thighs and extended toward the perineum. Gracilis tendons were identified and incised, and the muscles were dissected toward the groin. Simultaneously, the vessel pedicles were mobilized.

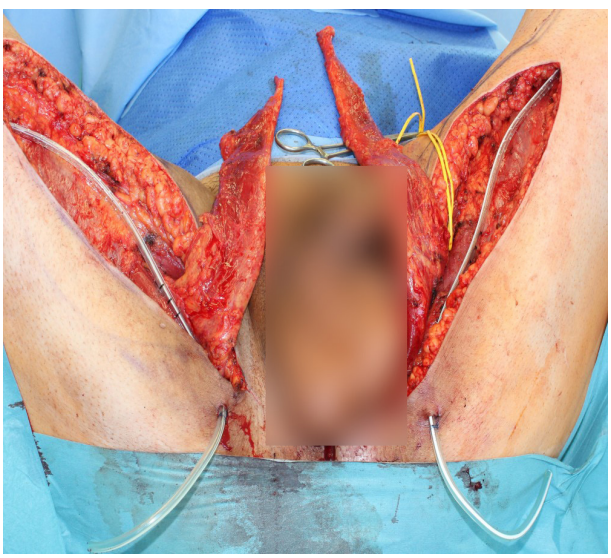

Fig 7: Two gracilis muscle flaps before tunneling them into perineal area

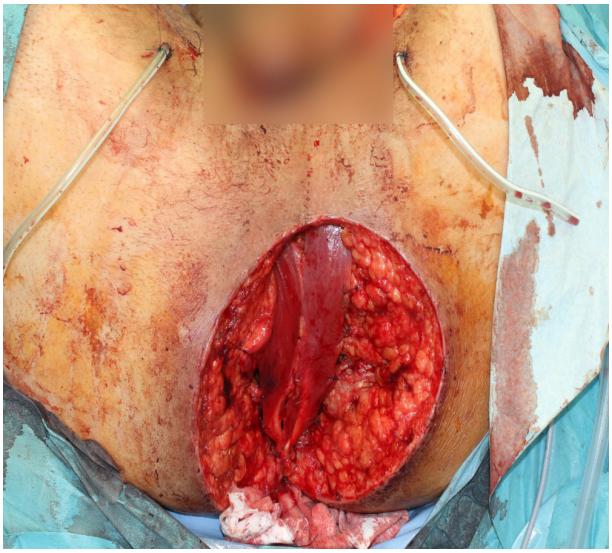

Fig 8: Gracilis muscle flaps fulfilling free space and make support for pelvic floor (lithotomy position)

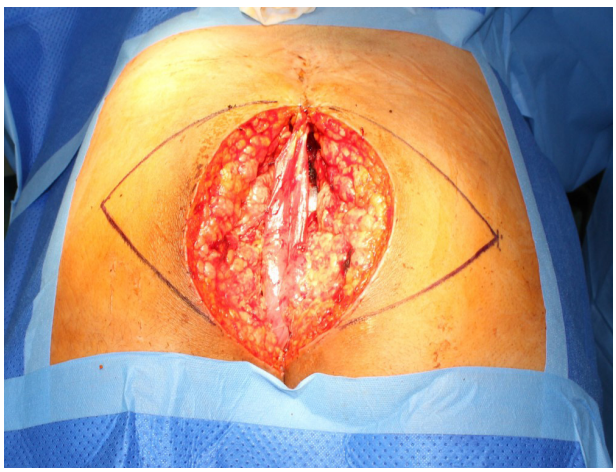

Fig 9: A scheme of bilateral V-Y advancement gluteal flaps

After the necrotic VRAM flap was removed, a 8 * 10 cm space defect in the pelvic diaphragm remained. The pelvic floor was covered with a 10 * 14 cm composite nonadhesive mesh, and the bilateral gracilis muscle flaps were tunneled to the defect space (Fig. 7). The flaps were sutured together and fixed to the perineal tissues covered with the synthetic mesh (Fig. 8).

The patient's position was changed from lithotomy to prone. To cover the defect, V-Y advancement flaps were harvested by making an approximately 10-cm-long skin incision, which was carried down to the fascia of the gluteus maximus muscle. When the flaps were elevated, a 4-5 cm skin and subcutaneous tissue advancement was achieved. The wound was closed in three layers without tension, and active wound

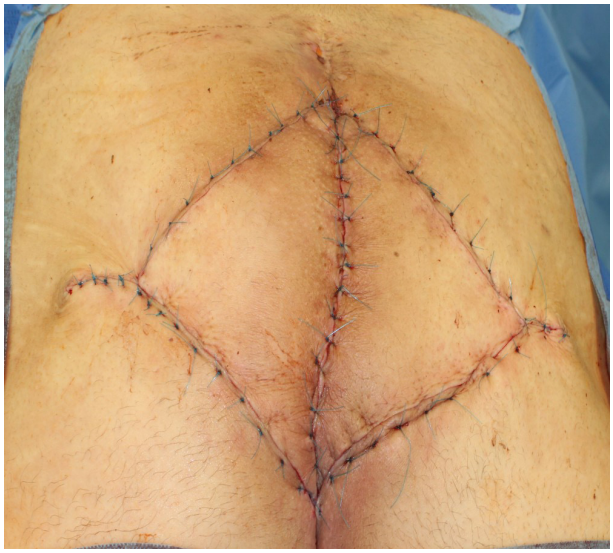

Fig 10: Completion of flap closure for remaining soft tissue defect (the patient in prone position)

drainage was used (Figs. 9 and 10). The total operation time was 405 min and the amount of blood loss was 200 mL.

The patient underwent intravenous antibiotic prophylaxis (1.0 g cefazolin and 500 mg metronidazole), thrombosis prevention (0.6 mL nadroparin), physiotherapy, and rehabilitation including activity modification. The patient was allowed to take a supine or standing position five days after surgery and was permitted to sit six weeks later. The postoperative period was uneventful, with the flaps showing adequate circulation. Two weeks later, primary healing of the wounds was observed (Fig. 11) and the patient was discharged from the hospital (total hospital stay: 26 days).

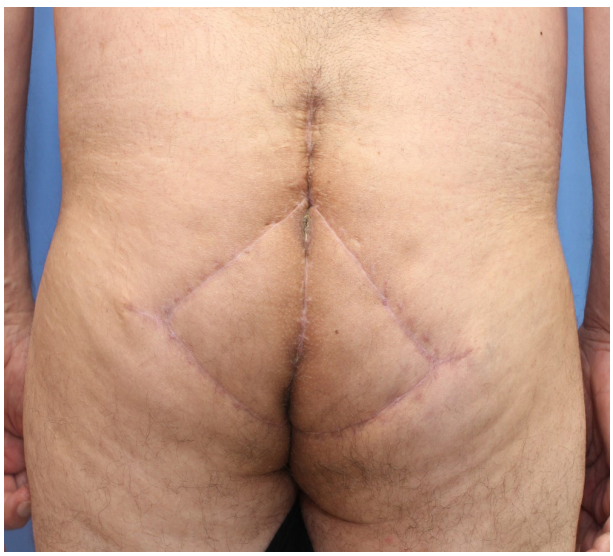

Fig 11: The result at 3-month follow up

DISCUSSION

To date, no standard guidelines exist on selecting reconstructive techniques for large sacral defects[7]. The vertical rectus abdominis flap is considered the primary option for repairing perineal defects via laparotomy, as it is relatively easy to harvest, provides a large bulk of healthy tissue to fill dead space, brings vascular tissue to the irradiated tumor bed, and provides a skin paddle for cutaneous wound closure [5,6,8-10]. It also reduces purulent collections and abscesses, and has a lower complication rate than other flaps[11]. Nonetheless, we encountered a case with total VRAM necrosis, which might have been associated with tension on the vessel pedicle. A similar case was previously reported by McMenamin *et al*[12]. Therefore, we considered that a muscle origin should be left intact and not dissected from the symphysis pubis to protect the vessel pedicle from tension or torsion[12]. When laparotomy is not required or VRAM flap necrosis occurs, the gracilis muscle flap is a reliable alternative for anorectal reconstruction, as it provides well-vascularized tissue for an inflamed and irritated area, thus creating better healing conditions. However, the gracilis flap is highly susceptible to vascular spasm and harvesting this flap as a musculocutaneous flap to be used as a skin paddle can be risky because it can be relatively tenuous. Moreover, if the cavity is large, gracilis muscles alone do not provide enough bulk to obliterate the dead space[4,10,13,14]. In this case, other choices of reconstruction should be considered. Therefore, V-Y advancement flaps should not be neglected, as they remain among the most frequently used flaps in all types of reconstructive surgery[15,16] and they can also be successfully used to repair large sacral soft tissue defects[17,18].

CONCLUSION

The aim of our paper was to present a complicated case of large perineal defect reconstruction after APR and to emphasize the importance of perineal wound reconstruction in collaboration with plastic surgeons. We suggest that when a large perineal defect appears after APR, immediate perineal reconstruction is important to reduce wound-healing complications. Although the VRAM flap is frequently used to reconstruct the perineal area, we presented another option for perineal reconstruction using gracilis muscle flaps combined with bilateral V-Y advancement gluteal flaps. We believe that this method of perineal wound reconstruction is also appropriate in cases in which VRAM flap necrosis occurs or when laparotomy is not performed.

ACKNOWLEDGMENTS

Author contribution: All authors co-ordinated research activities and were involved in the mnauscript preparation.

Conflict of interest: None

REFERENCES

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009; 59(4):225-49.
2. Foster JD, Pathak S, Smart NJ, Branagan G, Longman RJ, Thomas MG, *et al*. Reconstruction of the perineum following extralevator abdominoperineal excision for carcinoma of the lower rectum: a systematic review. Colorectal Dis 2012; 14(9):1052-9.
3. Bullard KM, Trudel JL, Baxter NN, Rothenberger DA. Primary perineal wound closure after preoperative radiotherapy and abdominoperineal resection has a high incidence of wound failure. Dis Colon Rectum 2005; 48(3):438-43.
4. Shibata D, Hyland W, Busse P, Kim HK, Sentovich SM, Steele G Jr, *et al*. Immediate reconstruction of the perineal wound with gracilis muscle flaps following abdominoperineal resection and intraoperative radiation therapy for recurrent carcinoma of the rectum. Ann Surg Oncol 1999; 6(1):33-7.
5. Buchel EW, Finical S, Johnson C. Pelvic reconstruction using vertical rectus abdominis musculocutaneous flaps. Ann Plast Surg 2004; 52(1):22-6.
6. Butler CE, Gundeslioglu AO, Rodriguez-Bigas MA. Outcomes of immediate vertical rectus abdominis myocutaneous flap reconstruction for irradiated abdominoperineal resection defects. J Am Coll Surg 2008; 206(4):694-703.
7. Miles WK, Chang DW, Kroll SS, Miller MJ, Langstein HN, Reece GP, *et al*. Reconstruction of large sacral defects following total sacrectomy. Plast Reconstr Surg 2000; 105(7):2387-94.
8. Chessin DB, Hartley J, Cohen AM, Mazumdar M, Cordeiro P, Disa J, *et al*. Rectus flap reconstruction decreases perineal wound complications after pelvic chemoradiation and surgery: a cohort study. Ann Surg Oncol 2005; 12(2):104-10.
9. Houvenaeghel G, Ghouti L, Moutardier V, Buttarelli M, Lelong B, Delpero JR. Rectus abdominis myocutaneous flap in radical oncopelvic surgery: a safe and useful procedure. Eur J Surg Oncol 2005; 31(10):1185-90.
10. Solomon MJ, Atkinson K, Quinn MJ, Eyers AA, Glenn DC. Gracilis myocutaneous flap to reconstruct large perineal defects. Int J Colorectal Dis 1996; 11(1):49-51.
11. Edington HD, Sugarbaker PH, McDonald HD. Management of the surgically traumatized, irradiated, and infected pelvis. Surgery 1988; 103(6):690-7.
12. McMenamin DM, Clements D, Edwards TJ, Fitton AR, Douie WJP. Rectus abdominis myocutaneous flaps for perineal reconstruction: modifications to the technique based on a large single-centre experience. Ann R Coll Surg Engl 2011; 93(5):375-81.
13. Arnold PG, Lovich SF, Pairolero PC. Muscle flaps in irradiated wounds: an account of 100 consecutive cases. Plast Reconstr Surg 1994; 93(2):324-7; discussion 328-9.
14. Chong TW, Balch GC, Kehoe SM, Margulis V, Saint-Cyr M. Reconstruction of large perineal and pelvic wounds using gracilis muscle flaps. Ann Surg Oncol 2015; 22(11):3738-44.
15. Zook EG, Van ALB, Russell RC, Moore JB. V-Y advancement flap for facial defects. Plast Reconstr Surg 1980; 65(6):786-97.
16. Ay A, Aytekin O, Aytekin A. Interdigitating fasciocutaneous gluteal V-Y advancement flaps for reconstruction of sacral defects. Ann Plast Surg 2003; 50(6):636-8.
17. Park C, Park BY. Fasciocutaneous V-Y advancement flap for repair of sacral defects. Ann Plast Surg 1988; 21(1):23-6.
18. Pu LLQ. Reconstruction of a large gluteal soft-tissue defect with the double-opposing V-Y fasciocutaneous advancement flap. Plast Reconstr Surg 2007; 119(2):599-603.

Selected Abstracts of Articles Published Elsewhere by Authors in Kuwait

Kuwait Medical Journal 2023; 55 (2): 179 - 181

Sex and obesity status modify the association between vitamin D and eczema among adolescents

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Pediatr Res. 2023 May 12. doi: 10.1038/s41390-023-02641-y. Online ahead of print.

BACKGROUND

Epidemiologic studies have reported inconsistent associations between vitamin D and eczema. This study sought to assess whether sex and obesity status could modify the association between vitamin D and eczema.

METHODS

A cross-sectional study enrolled 763 adolescents in Kuwait. 25-hydroxyvitamin D (25(OH)D) was measured in venous blood. Current eczema was defined according to clinical history and characteristic morphology and distribution.

RESULTS

In sex-stratified analysis, decreased 25(OH)D levels were associated with increased current eczema prevalence among males (adjusted odds ratio (aOR)tertile 1 vs. tertile 3: 2.14, 95% confidence intervals (CI): 1.07-4.56), but not among females (aORtertile 1 vs. tertile 3: 1.08, 95% CI: 0.71-1.66). Further stratification by obesity status showed that lower 25(OH)D levels were associated with increased current eczema prevalence among overweight/obese males (per 10-unit decrease in 25(OH)D levels: aOR: 1.70, 95% CI: 1.17-2.46). Such an association was weaker and statistically non-significant among overweight/obese females (per 10-unit decrease in 25(OH)D levels: aOR: 1.26, 95% CI: 0.93-1.70).

CONCLUSIONS

Sex and obesity status modified the association between vitamin D levels and eczema, with an inverse association observed among overweight/obese males, but not among overweight/obese females. These results suggest that preventive and clinical management strategies could vary by sex and obesity status.

IMPACT

The current study showed that sex and obesity modify the association between vitamin D and eczema among adolescents. An inverse association between vitamin D and eczema was observed among overweight/obese males, but this association was not as pronounced among overweight/obese females. Vitamin D was not associated with eczema among underweight/normal weight males and females. The identification of effect modification by sex and obesity status add to the current scientific knowledge and further highlight the complexity of the association between vitamin D and eczema. These results may promote a more individualized approach to the future prevention and clinical management of eczema.

Operative treatment of distal radius fractures involving the volar rim-A systematic review of outcomes and complications

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Eur J Orthop Surg Traumatol. 2023 May 6. doi: 10.1007/s00590-023-03558-2. Online ahead of print.

PURPOSE
Distal radius fractures involving the volar rim are a subset of unstable and extremely distal fractures involving the volar lunate and/or scaphoid facets. Volar rim fractures (VRF) are challenging to manage and different treatment options have been described. This study aimed to compare outcomes and assess the rates of complications and implant removal for different treatment methods of wrist fractures involving VRF.

METHODS
A systematic review of studies published in MEDLINE, EMBASE, Web of Science and Cumulative Index to Nursing and Allied Health literature (CINAHL) was conducted to assess the operative outcomes of VRF. Data on patient demographics, implant usage, postoperative outcomes, complications, and implant removal were compiled.

RESULTS
Twenty-six studies met the inclusion criteria with a total of 617 wrists. The most commonly used implants were 2.4 mm variable-angle volar rim plate (DePuy Synthes) (17.5%), Acu-Loc II (Acumed) (14%) and standalone hook plates (13%). The average outcome measures were Q-DASH (10.9 ± 7), MWS (85.8 ± 7.5), PRWE (15.9 ± 12.1), and DASH (14 ± 8.5). The overall complication rate was 14% (n = 87), with 44% (n = 38) involving flexor tendon problems. The implant removal rate was 22%, with routine removal being performed in 54% and non-routine removal in 46% of cases.

CONCLUSION
The current treatment of VRF yields favorable functional outcomes across different treatment options. However, these fractures have a high rate of complications and re-interventions, particularly for symptomatic implants.

Long-term Outcomes of Sleeve Gastrectomy in Adolescent Patients: The Effect of Weight Loss in Younger Years to Outcomes in Adulthood

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BMC Surg. 2023 Apr 28;23(1):103. doi: 10.1186/s12893-023-02006-6.

BACKGROUND
Childhood obesity is associated with a variety of complications that see their light throughout adulthood. Due to the serious side effects of these morbidities, early intervention is essential. Laparoscopic sleeve gastrectomy (SG) is a safe and effective procedure for the treatment of obesity, however, the long-term data on its use in adolescents is lacking in the literature.

METHODS
A retrospective analysis was conducted on all patients that underwent SG aged between 12 and 21 years old at a public hospital in Kuwait. Data on their weight and comorbidities was collected and analyzed.

RESULTS
164 adolescent patients with a mean age of 19 underwent SG. 71% of the patients were female, while the mean weight at surgery was 128.6 kg, corresponding to a BMI of 47.8 Kg/m2. 32% of patients had a starting BMI more than 50, while 6.7% had a BMI over 60. The highest weight loss was achieved at 18 months post-op, corresponding to an EWL of 82.66%. On long-term follow-up, weight loss was maintained over the 13 years post-op. Obstructive sleep apnea resolved in 75% of the patients while hypertension persisted in the 2 patients who were diagnosed with it pre-op. 21 patients developed gastro-esophageal reflux disease 5.7 years post-op, while 20 patients were treated for gall bladder stones 4.4 years post-op.

CONCLUSION
It is of ample importance to tackle obesity during childhood before complications ensue later in life. Bariatric surgery, specifically SG, has been found to be an effective and safe weight loss tool, with sustained long-term weight maintenance and resolution of early comorbidities.

Pain, Pattern and Polytrauma - Predictors of Sexual Dysfunction in Pelvic Fractures: A Retrospective Multicenter Analysis

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Arch Bone Jt Surg. 2023;11(4):263-269. doi: 10.22038/ABJS.2022.57958.2869.

OBJECTIVES
In the local and cultural setting of high trauma rates and a reserved outlook on sexual function, this study examines the incidence and underlying factors of sexual dysfunction (SD) following pelvic fractures.

METHODS
A Multi-center retrospective cohort analysis performed in two general hospitals and one tertiary orthopedic center with collection between 2017 and 2019. Consecutive patients with pelvic fractures between January 2017 and February 2019 were followed up at 18-24 months to screen for new-onset SD using the International Index of Erectile Function-5 (IIEF-5) and Female-Sexual-Function-Index-6 (FSFI-6). Additional variables include age, sex, Young-Burgess classification, urogenital injury, injury severity score, persisting pain, sacroiliac disruption, intervention and if sexual health was discussed or patient referred for sexual healthcare.

RESULTS
One-hundred and sixty-five patients (n = 165) were included, (83%) male, (16%) female with a mean age of 35.1 years (Range 18-55). Fracture patterns included lateral compression (LC) (51.5%), anteroposterior compression (APC) (27.7%), and vertical shear (VS) (20.6%). The urogenital injury occurred in 10.3%. The mean IIEF-5 and FSFI-6 scores were 20.8 and 24.7 in males and females, respectively. A total of 40 males (29%) scored below the 21 cut-off scores for SD, while only one female (3.7%) scored below the corresponding score of 19. Of all participants reporting sexual dysfunction, 56% discussed sexual health with their providers, while 46% of these patients were referred for further management. Significant predictive factors for SD using a multivariate logistic regression model include increasing age (OR-1.093, p = 0.006), APC III (OR 88.887, p = 0.006), VS (OR-15.607, p = 0.020), persisting pain (OR 3.600, p = 0.021) and increasing injury severity score (OR 1.184, p <0.001).

CONCLUSION
SD is common among pelvic fractures, and risk factors include APC or VS type fractures, increasing age, increasing injury severity score, and persisting pain. Providers should ensure patients are screened for SD and referred appropriately as patients may not willingly disclose underlying symptoms.

Forthcoming Conferences and Meetings

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Vineetha Elizabeth Mammen

Kuwait Medical Journal 2023; 55 (2): 182 - 191

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Event Website: http://scienceplus.us/Conference/26154/ICMHS/

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United Arab Emirates, Dubai
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/21578/ICHCG/

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1532nd International Conference on Recent Advances in **Medical and Health Sciences**
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Event Website: http://itrgroup.net/Conference/931/ICV/

1564th International Conferences on **Medical and Health Science**
Jun 22, 2023
Spain, Madrid
Email: info@theires.org
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1578th International Conference on Recent Advances in **Medical Science**
Jun 23, 2023
Spain, Barcelona
Email: info@theiier.org
Event Website: http://theiier.org/Conference2023/Spain/3/ICRAMS/

1550th International Conference on **Medical, Biological and Pharmaceutical Scienc**es
Jun 24, 2023
South Africa, Cape Town
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Event Website: http://iastem.org/Conference2023/SouthAfrica/1/ICMBPS/

International Conference on Advances in **Health and Medical Science**
Jun 24, 2023
Japan, Tokyo
Email: info.saard.org@gmail.com
Event Website: http://saard.org/Conference/2454/ICAHMS/

International Conference on Advances in **Health and Medical Science**
Jun 25, 2023
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Event Website: http://saard.org/Conference/2190/ICAHMS/

International Virtual Conference on **COVID-19** and its Effect
Jun 26, 2023
Japan, Kyoto
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International Conference on **Medical, Pharmaceutical and Health Sciences**
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Event Website: http://gsrd.co/Conference/11134/ICMPH/

1552nd International Conference on **Medical, Biological and Pharmaceutical Sciences**
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International Conference on **Medical and Biological Engineering**
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Event Website: http://technoconferences.com/Conference/10643/ICMBE/

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Jun 28, 2023
Canada, Ottawa
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1581st International Conference on Recent Advances in **Medical Science**
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1505th International Conference on Recent Advances in **Medical and Health Sciences**
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International Research Conference on **COVID-19** and its Impact on **Mental Health**
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1549th International Conference on Recent Advances in **Medical and Health Sciences**
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1563rd International Conference on **Medical, Biological and Pharmaceutical Sciences**
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Saudi Arabia, Jeddah
Email: info@iastem.org
Event Website: http://iastem.org/Conference2023/SaudiArabia/5/ICMBPS/

International Conference on Recent Advances in **Medical Science**
Jul 16, 2023
United States of America, Honolulu
Email: info@theiier.org
Event Website: http://theiier.org/Conference2023/US/63/ICRAMS/

World **Disability and Rehabilitation** Conference
Jul 17, 2023
China, Chengdu
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/37850/WDRC/

1593rd International Conference on Recent Advances in **Medical Science**
Jul 18, 2023
United Kingdom, London
Email: info@theiier.org
Event Website: http://theiier.org/Conference2023/UK/3/ICRAMS/

International Video Conference on **Healthcare**
Jul 19, 2023
United Arab Emirates, Abu Dhabi
Email: info.conferenceonline@gmail.com
Event Website: http://conferenceonline.net/Conference/1135/IVCH/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences**
Jul 20, 2023
Turkey, Istanbul
Email: info.irfconference@gmail.com
Event Website: http://irfconference.org/Conference/17848/ICRAMNH/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Jul 21, 2023
Argentina, Buenos Aires
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference/10930/ICMPH/

International Conference on Recent Advances in **Medical Science**
Jul 22, 2023
United States of America, Dallas
Email: info@theiier.org
Event Website: http://theiier.org/Conference2023/US/67/ICRAMS/

International Conference on **Medical Ethics and Professionalism**
Jul 23, 2023
Indonesia, Surabaya
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/23920/ICMEP/

International Conference on **Medical Health Science, Pharmacology and Bio Technology**
Jul 24, 2023
Italy, Rome
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/18534/ICMPB/

International Conference on **Cell and Tissue Science**
Jul 26, 2023
United Arab Emirates, Al Ain
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/42515/ICCTS/

International Conference on **Cell and Tissue Science**
Jul 27, 2023
Philippines, Caloocan
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/42491/ICCTS/

International Conference on **Nursing Ethics and Medical Ethics**
Jul 28, 2023
Japan, Saitama
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/22908/ICNEME/

International Conference on **Nutrition and Food Science**
Jul 28, 2023
Canada, Toronto
Email: igrnetconference@gmail.com
Event Website: http://igrnet.org/Conference/754/ICNFS/

International Conference on Recent Advances in **Medical and Health Sciences**
Jul 29, 2023
India, New Delhi
Email: info@academicsworld.org
Event Website: https://academicsworld.org/Conference2023/India/9/ICRAMHS/

International conference on **Medical Health Science, Pharmacology and Bio Technology**
Aug 01, 2023
United States of America, New York
Email: papers.issrd@gmail.com
Event Website: http://issrd.org/Conference/18498/ICMPB/

1386th International Conference on **Medical and Health Science**
Aug 01, 2023
United Arab Emirates, Dubai
Email: info@researchfora.com
Event Website: http://researchfora.com/Conference2023/UAE/5/ICMHS/

1568th International Conference on Recent Advances in **Medical and Health Sciences**
Aug 02, 2023
United Arab Emirates, Sharjah
Email: info@academicsworld.org
Event Website: https://academicsworld.org/Conference2023/UAE/4/ICRAMHS/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Aug 03, 2023
Germany, Berlin
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference/10810/ICMPH/

International Conference on Advances in **Health and Medical Science**
Aug 04, 2023
Scotland, Glasgow
Email: info.saard.org@gmail.com
Event Website: http://saard.org/Conference/2146/ICAHMS/

International Conference on Latest Research on **Corona Virus and its Vaccine**
Aug 04, 2023
United States of America, New York
Email: info.researchconferences@gmail.com
Event Website: http://researchconferences.in/Conference/3863/ICRCVV/

International Conference on **Medical, Medicine and Health Sciences**
Aug 05, 2023
Egypt, Cairo
Email: contact.iierd@gmail.com
Event Website: http://iierd.com/Conference/2586/ICMMH/

World **Disability and Rehabilitation** Conference
Aug 06, 2023
Vietnam, Hanoi
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/37742/WDRC/

1469th International Conference on **Food Microbiology and Food Safety**
Aug 07, 2023
United Kingdom, London
Email: info@theires.org
Event Website: http://theires.org/Conference2023/UK/6/ICFMFS/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Aug 09, 2023
Qatar, Doha
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference/10750/ICMPH/

International Conference on **Cardiology and Diabetes**
Aug 13, 2023
France, Paris
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/557/ICCD/

International Conference on Recent Advances in **Medical, Medicine and Health Sciences**
Aug 14, 2023
Saudi Arabia, Medina
Email: contact.wrfer@gmail.com
Event Website: http://wrfer.org/Conference/25414/ICRAMMHS/

International Conference on Recent Advances in **Medical Science**
Aug 14, 2023
United States of America, San Francisco
Email: info@theiier.org
Event Website: http://theiier.org/Conference2023/US/71/ICRAMS/

International Conference on **Medical and Biological Engineering**
Aug 15, 2023
India, Raipur, Chhattisgarh
Email: papers.techno@gmail.com
Event Website: http://technoconferences.com/Conference/11186/ICMBE/

World Conference on **Pharma Industry and Medical Devices**
Aug 15, 2023
United Arab Emirates, Sharjah
Email: info.ifearpworld@gmail.com
Event Website: http://ifearp.org/Conference/8612/WCPIMD/

1574th International Conference on **Medical and Biosciences**
Aug 16, 2023
United States of America, Boston
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2023/USA/12/ICMBS/

1433rd International Conference on **Pharma and Food**
Aug 17, 2023
Finland, Helsinki
Email: info@academicsera.com
Event Website: http://academicsera.com/Conference2023/Finland/1/ICPAF/

International Conference on **Virology**
Aug 18, 2023
Japan, Kyoto
Email: papers.itrgroup@gmail.com
Event Website: http://itrgroup.net/Conference/1007/ICV/

World **Disability and Rehabilitation** Conference
Aug 19, 2023
India, Goa
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/42262/WDRC/

World **Disability and Rehabilitation** Conference
Aug 20, 2023
New Zealand, Auckland
Email: papers.asar@gmail.com
Event Website: http://asar.org.in/Conference/37607/WDRC/

1589th International Conference on **Medical and Health Sciences**
Aug 20, 2023
Singapore, Singapore
Email: info@iserd.co
Event Website: http://iserd.co/Conference2023/Singapore/2/ICMHS/

1577th International Conference on **Medical and Biosciences**
Aug 21, 2023
Turkey, Antalya
Email: info@researchworld.org
Event Website: http://researchworld.org/Conference2023/Turkey/3/ICMBS/

International Conference on **Cell and Tissue Science**
Aug 21, 2023
Scotland, Dundee
Email: info@conferencefora.org
Event Website: http://conferencefora.org/Conference/42017/ICCTS/

International Conference on **Healthcare and Clinical Gerontology**
Aug 24, 2023
China, Hong Kong
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/20680/ICHCG/

1401st International Conference on **Medical and Health Science**
Aug 24, 2023
Australia, Melbourne
Email: info@researchfora.com
Event Website: http://researchfora.com/Conference2023/Australia/5/ICMHS/

International Conference on **Medicine, Nursing and Healthcare**
Aug 25, 2023
Singapore, Singapore
Email: info@yanjiuconference.com
Event Website: http://yanjiuconference.com/Conference/2275/ICMNH/

International Virtual Conference on **Medical Biological and Pharmaceutical Science**
Aug 26, 2023
United Kingdom, London
Email: info.conferenceonline@gmail.com
Event Website: http://conferenceonline.net/Conference/1214/IVCMBPS/

International Conference on **Medical and Health Sciences**
Aug 27, 2023
United Arab Emirates, Dubai
Email: papers.academicsconference@gmail.com
Event Website: http://academicsconference.com/Conference/28576/ICMHS/

International Conference on **Cardiology and Diabetes**
Aug 27, 2023
Germany, Berlin
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/541/ICCD/

World Conference on **Pharma Industry and Medical Devices**
Aug 28, 2023
Saudi Arabia, Mecca
Email: info.ifearpworld@gmail.com
Event Website: http://ifearp.org/Conference/8540/WCPIMD/

International Conference on **Medical and Health Sciences**
Aug 30, 2023
Qatar, Doha
Email: info.inderscience.org@gmail.com
Event Website: http://inderscience.org/Conference/695/ICMHS/

1386th International Conference on **Medical and Health Science**
Aug 01, 2023
United Arab Emirates, Dubai
Email: info@researchfora.com
Event Website: http://researchfora.com/Conference2023/UAE/5/ICMHS/

1555th International Conference on **Science, Health and Medicine**
Aug 02, 2023
United Arab Emirates, Abu Dhabi
Email: info@iser.co
Event Website: http://iser.co/Conference2023/UAE/4/ICSHM/

International Conference on **Healthcare and Clinical Gerontology**
Aug 04, 2023
Korea (South), Busan
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/20914/ICHCG/

International Conference on **Medical and Health Sciences**
Aug 05, 2023
India, Mumbai, Maharashtra
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/27154/ICMHS/

International Conference on **Medical, Pharmaceutical and Health Sciences**
Aug 06, 2023
Japan, Yokohama
Email: info.gsrd@gmail.com
Event Website: http://gsrd.co/Conference/13343/ICMPH/

International Conference on **Medical, Medicine and Health Sciences**
Aug 06, 2023
Turkey, Istanbul
Email: contact.iierd@gmail.com
Event Website: http://iierd.com/Conference/2582/ICMMH/

1571st International Conference on Recent Advances in **Medical and Health Sciences**
Aug 07, 2023
Japan, Tokyo
Email: info@academicsworld.org
Event Website: https://academicsworld.org/Conference2023/Japan/8/ICRAMHS/

1561st International Conference on **Science, Health and Medicine**
Aug 11, 2023
Egypt, Cairo
Email: info@iser.co
Event Website: http://iser.co/Conference2023/Egypt/2/ICSHM/

1393rd International Conference on **Medical and Health Science**
Aug 12, 2023
France, Paris
Email: info@researchfora.com
Event Website: http://researchfora.com/Conference2023/France/3/ICMHS/

3rd International Conference on **Environment and Life Science**
Aug 13, 2023
United Arab Emirates, Dubai
Email: info.isfecc@gmail.com
Event Website: https://isfecc.org/Conference/78/ICELS/

International Conference on Recent Advances in **Medical and Health Sciences**
Aug 13, 2023
Saudi Arabia, Jeddah
Email: info@academicsworld.org
Conference Website:https://academicsworld.org/Conference2023/SaudiArabia/15/ICRAMHS/

International Virtual Conference on **COVID-19 and its Effect**
Aug 14, 2023
Malaysia, Putrajaya
Email: info.conferenceonline@gmail.com
Event Website: http://conferenceonline.net/Conference/1266/IVCCE/

International Virtual Conference on **COVID-19 and its Effect**
Aug 16, 2023
Malaysia, Kuala Lumpur
Email: info.conferenceonline@gmail.com
Event Website: http://conferenceonline.net/Conference/1254/IVCCE/

International Conference on **Healthcare and Clinical Gerontology**
Aug 17, 2023
United States of America, Kansas
Email: info.sciencefora@gmail.com
Event Website: http://sciencefora.org/Conference/20758/ICHCG/

International Conference on Latest Research on **Corona Virus and its Vaccine**
Aug 19, 2023
United Arab Emirates, Dubai
Email: info.researchconferences@gmail.com
Event Website: http://researchconferences.in/Conference/3808/ICRCVV/

1566th International Conference on **Science, Health and Medicine**
Aug 19, 2023
United States of America, Cambridge
Email: info@iser.co
Event Website: http://iser.co/Conference2023/USA/13/ICSHM/

International Conference on **Medical and Health Sciences**
Aug 20, 2023
United Kingdom, Cambridge
Email: papers.scienceplus@gmail.com
Event Website: http://scienceplus.us/Conference/25962/ICMHS/

International Conference on Advances in **Health and Medical Science**
Aug 20, 2023
Thailand, Phuket
Email: info.saard.org@gmail.com
Event Website: http://saard.org/Conference/2542/ICAHMS/

1399th International Conference on **Medical and Health Science**
Aug 21, 2023
Italy, Venice
Email: info@researchfora.com
Event Website: http://researchfora.com/Conference2023/Italy/4/ICMHS/

International Conference on Recent Advancement in **Medical Education, Nursing, and Health Sciences**
Aug 22, 2023
Australia, Sydney
Email: info.irfconference@gmail.com
Event Website: http://irfconference.org/Conference/17743/ICRAMNH/

International Conference on Latest Research on **Corona Virus and its Vaccine**
Aug 23, 2023
India, Pune, Maharashtra
Email: info.researchconferences@gmail.com
Event Website: http://researchconferences.in/Conference/3793/ICRCVV/

1591st International Conference on **Medical and Health Sciences**
Aug 23, 2023
Romania, Bucharest
Email: info@iserd.co
Event Website: http://iserd.co/Conference2023/Romania/1/ICMHS/

1583rd International Conference on Recent Advances in **Medical and Health Sciences**
Aug 25, 2023
France, Paris
Email: info@academicsworld.org
Event Website: https://academicsworld.org/Conference2023/France/2/ICRAMHS/

International Conference on Recent advancement in **Medical Education, Nursing, and Health Sciences**
Aug 26, 2023
United Arab Emirates, Dubai
Email: info.irfconference@gmail.com
Event Website: http://irfconference.org/Conference/17736/ICRAMNH/

International Conference on **Nursing Science and Healthcare**
Aug 26, 2023
United States of America, Washington, D.C.
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/547/ICNSH/

International Conference on **Nursing Science and Healthcare**
Aug 27, 2023
Germany, Berlin
Email: info.iared.org@gmail.com
Event Website: http://iared.org/Conference/539/ICNSH/

International Conference on **Science, Health and Medicine**
Aug 28, 2023
Canada, Calgary
Email: info@iser.co
Event Website: http://iser.co/Conference2023/Canada/38/ICSHM/

International Conference on **Diabetes and Endocrinology**
Aug 29, 2023
Swaziland, Geneva
Email: info.diabetesworld@gmail.com
Event Website: http://diabetesworld.net/Conference/58/ICDE/

International Conference on **Vaccine Research, Immunology and Clinical Trials**
Aug 30, 2023
United States of America, New York
Email: info@meetingfora.com
Event Website: http://meetingfora.com/Conference/95/ICVRICT/

International Conference on **Medical and Health Sciences**
Aug 31, 2023
Hong Kong, Hong Kong
Email: info.inderscience.org@gmail.com
Event Website: http://inderscience.org/Conference/687/ICMHS/

WHO-Facts Sheet

1. Dementia
2. Guillain-Barre syndrome
3. Listeriosis
4. Natural toxins in food
5. Sepsis

Compiled and edited by
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1. Dementia

KEY FACTS

- Currently more than 55 million people have dementia worldwide, over 60% of whom live in low-and middle-income countries. Every year, there are nearly 10 million new cases.
- Dementia results from a variety of diseases and injuries that affect the brain. Alzheimer disease is the most common form of dementia and may contribute to 60–70% of cases.
- Dementia is currently the seventh leading cause of death and one of the major causes of disability and dependency among older people globally.
- In 2019, dementia cost economies globally 1.3 trillion US dollars, approximately 50% of these costs are attributable to care provided by informal carers (e.g. family members and close friends), who provide on average 5 hours of care and supervision per day.
- Women are disproportionately affected by dementia, both directly and indirectly. Women experience higher disability-adjusted life years and mortality due to dementia, but also provide 70% of care hours for people living with dementia.

Overview

Dementia is a term for several diseases that affect memory, thinking, and the ability to perform daily activities. The illness gets worse over time. It mainly affects older people but not all people will get it as they age.

Things that increase the risk of developing dementia include:

- age (more common in those 65 or older)
- high blood pressure (hypertension)
- high blood sugar (diabetes)
- being overweight or obese
- smoking
- drinking too much alcohol
- being physically inactive
- being socially isolated
- depression.

Dementia is a syndrome that can be caused by a number of diseases which over time destroy nerve cells and damage the brain, typically leading to deterioration in cognitive function (i.e. the ability to process thought) beyond what might be expected from the usual consequences of biological ageing. While consciousness is not affected, the impairment in cognitive function is commonly accompanied, and occasionally preceded, by changes in mood, emotional control, behaviour, or motivation.

Dementia has physical, psychological, social and economic impacts, not only for people living with dementia, but also for their carers, families and society at large. There is often a lack of awareness and understanding of dementia, resulting in stigmatization and barriers to diagnosis and care.

Signs and symptoms

Changes in mood and behaviour sometimes happen even before memory problems occur. Symptoms get worse over time. Eventually, most people with dementia will need others to help with daily activities.

Early signs and symptoms are:

- forgetting things or recent events
- losing or misplacing things
- getting lost when walking or driving
- being confused, even in familiar places
- losing track of time
- difficulties solving problems or making decisions
- problems following conversations or trouble finding words

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- difficulties performing familiar tasks
- misjudging distances to objects visually.

Common changes in mood and behaviour include:

- feeling anxious, sad, or angry about memory loss
- personality changes
- inappropriate behaviour
- withdrawal from work or social activities
- being less interested in other people's emotions.

Dementia affects each person in a different way, depending upon the underlying causes, other health conditions and the person's cognitive functioning before becoming ill.

Most symptoms become worse over time, while others might disappear or only occur in the later stages of dementia. As the disease progresses, the need for help with personal care increases. People with dementia may not be able to recognize family members or friends, develop difficulties moving around, lose control over their bladder and bowls, have trouble eating and drinking and experience behaviour changes such as aggression that are distressing to the person with dementia as well as those around them.

Common forms of dementia

Dementia is caused by many different diseases or injuries that directly and indirectly damage the brain. Alzheimer disease is the most common form and may contribute to 60–70% of cases. Other forms include vascular dementia, dementia with Lewy bodies (abnormal deposits of protein inside nerve cells), and a group of diseases that contribute to frontotemporal dementia (degeneration of the frontal lobe of the brain). Dementia may also develop after a stroke or in the context of certain infections such as HIV, as a result of harmful use of alcohol, repetitive physical injuries to the brain (known as chronic traumatic encephalopathy) or nutritional deficiencies. The boundaries between different forms of dementia are indistinct and mixed forms often co-exist.

Treatment and care

There is no cure for dementia, but a lot can be done to support both people living with the illness and those who care for them.

People with dementia can take steps to maintain their quality of life and promote their well-being by:

- being physically active
- taking part in activities and social interactions that stimulate the brain and maintain daily function.

In addition, some medications can help manage dementia symptoms:

- Cholinesterase inhibitors like donepezil are used to treat Alzheimer disease.
- NMDA receptor antagonists like memantine are used for severe Alzheimer disease and vascular dementia.
- Medicines to control blood pressure and cholesterol can prevent additional damage to the brain due to vascular dementia.
- Selective serotonin reuptake inhibitors (SSRIs) can help with severe symptoms of depression in people living with dementia if lifestyle and social changes don't work, but these should not be the first option.

If people living with dementia are at risk of hurting themselves or others, medicines like haloperidol and risperidone can help, but these should never be used as the first treatment

Self-care

For those diagnosed with dementia, there are things that can help manage symptoms:

- Stay physically active.
- Eat healthily.
- Stop smoking and drinking alcohol.
- Get regular check-ups with your doctor.
- Write down everyday tasks and appointments to help you remember important things.
- Keep up your hobbies and do things that you enjoy.
- Try new ways to keep your mind active.
- Spend time with friends and family and engage in community life.

Plan ahead of time. Over time, it may be harder to make important decisions for yourself or your finances:

- Identify people you trust to support you in making decisions and help you communicate your choices.
- Create an advance plan to tell people what your choices and preferences are for care and support.
- Bring your ID with your address and emergency contacts when leaving the house.
- Reach out to family and friends for help.
- Talk to people you know about how they can help you.
- Join a local support group.

It is important to recognize that providing care and support for a person living with dementia can be challenging, impacting the carer's own health and well-being. As someone supporting a person living with dementia, reach out to family members, friends, and professionals for help. Take regular breaks and look after yourself. Try stress management techniques such as mindfulness-based exercises and seek professional help and guidance if needed.

Risk factors and prevention

Although age is the strongest known risk factor for dementia, it is not an inevitable consequence of biological ageing. Further, dementia does not exclusively affect older people – young onset dementia (defined as the onset of symptoms before the age of 65 years) accounts for up to 9% of cases. Studies show that people can reduce their risk of cognitive decline and dementia by being physically active, not

smoking, avoiding harmful use of alcohol, controlling their weight, eating a healthy diet, and maintaining healthy blood pressure, cholesterol and blood sugar levels. Additional risk factors include depression, social isolation, low educational attainment, cognitive inactivity and air pollution.

Human rights

Unfortunately, people living with dementia are frequently denied the basic rights and freedoms available to others. In many countries, physical and chemical restraints are used extensively in care homes for older people and in acute-care settings, even when regulations are in place to uphold the rights of people to freedom and choice.

An appropriate and supportive legislative environment based on internationally-accepted human rights standards is required to ensure the highest quality of care for people with dementia and their carers.

WHO response

WHO recognizes dementia as a public health priority. In May 2017, the World Health Assembly endorsed the Global action plan on the public health response to dementia 2017-2025. The Plan provides a comprehensive blueprint for action – for policy-makers, international, regional and national partners, and WHO in the following areas: addressing dementia as a public health priority; increasing awareness of dementia and creating a dementia-inclusive society; reducing the risk of dementia; diagnosis, treatment and care; information systems for dementia; support for dementia carers; and, research and innovation

To facilitate the monitoring of the global dementia action plan, WHO developed the Global Dementia Observatory (GDO), a data portal that collates country data on 35 key dementia indicators across the global action plan's seven strategic areas. As a complement to the GDO, WHO launched the GDO Knowledge Exchange Platform, which is a repository of good practices examples in the area of dementia with the goal of fostering mutual learning and multi-directional exchange between regions, countries and individuals to facilitate action globally.

2. Guillain-Barre syndrome

KEY FACTS

- Guillain-Barré syndrome (GBS) is a rare condition in which a person's immune system attacks the peripheral nerves.
- People of all ages can be affected, but it is more common in adults and in males.
- Most people recover fully from even the most severe cases of Guillain-Barré syndrome.
- Severe cases of Guillain-Barré syndrome are rare, but can result in near-total paralysis.
- Guillain-Barré syndrome is potentially life-threatening. People with Guillain-Barré syndrome should be treated and monitored; some may need intensive care. Treatment includes supportive care and some immunological therapies.

Introduction

In Guillain-Barré syndrome, the body's immune system attacks part of the peripheral nervous system. The syndrome can affect the nerves that control muscle movement as well as those that transmit pain, temperature and touch sensations. This can result in muscle weakness and loss of sensation in the legs and/or arms.

It is a rare condition, and while it is more common in adults and in males, people of all ages can be affected.

Symptoms

Symptoms typically last a few weeks, with most individuals recovering without long-term, severe neurological complications.

- The first symptoms of Guillain-Barré syndrome include weakness or tingling sensations. They usually start in the legs, and can spread to the arms and face.
- For some people, these symptoms can lead to paralysis of the legs, arms, or muscles in the face. In 20%–30 % of people, the chest muscles are affected, making it hard to breathe.
- The ability to speak and swallow may become affected in severe cases of Guillain-Barré syndrome. These cases are considered life-threatening, and affected individuals should be treated in intensive-care units.
- Most people recover fully from even the most severe cases of Guillain-Barré syndrome, although some continue to experience weakness.
- Even in the best of settings, 3%–5% of Guillain-Barré syndrome patients die from complications, which can include paralysis of the muscles that control breathing, blood infection, lung clots, or cardiac arrest.

Causes

Guillain-Barré syndrome is often preceded by an infection. This could be a bacterial or viral infection. Guillain-Barré syndrome may also be triggered by vaccine administration or surgery.

In the context of Zika virus infection, unexpected increase in cases of Guillain-Barré syndrome has

been described in affected countries. The most likely explanation of available evidence from outbreaks of Zika virus infection and Guillain-Barré syndrome is that Zika virus infection is a trigger of Guillain-Barré syndrome.

Diagnosis

Diagnosis is based on symptoms and findings on neurological examination including diminished or loss of deep-tendon reflexes. A lumbar puncture may be done for supportive information, though should not delay treatment. Other tests, such as blood tests, to identify the underlying trigger are not required to make the diagnosis of GBS and should not delay treatment.

Treatment and care

The following are recommendations for treatment and care of people with Guillain-Barré syndrome:

- Guillain-Barré syndrome is potentially life-threatening. GBS patients should be hospitalized so that they can be monitored closely.
- Supportive care includes monitoring of breathing, heartbeat and blood pressure. In cases where a patient's ability to breathe is impaired, he or she is usually put on a ventilator. All GBS patients should be monitored for complications, which can include abnormal heart beat, infections, blood clots, and high or low blood pressure.
- There is no known cure for GBS. But treatments can help improve symptoms of GBS and shorten its duration.
- Given the autoimmune nature of the disease, its acute phase is typically treated with immunotherapy, such as plasma exchange to remove antibodies from the blood or intravenous immunoglobulin. It is most often beneficial when initiated 7 to 14 days after symptoms appear.
- In cases where muscle weakness persists after the acute phase of the illness, patients may require rehabilitation services to strengthen their muscles and restore movement.

WHO Response

WHO is supporting countries to manage GBS in context of Zika virus infection by:

- Enhancing surveillance of GBS in Zika affected countries.
- Providing guidelines for the assessment and management of GBS.
- Supporting countries to implement guidelines and strengthen health systems to improve the management of GBS cases.
- Defining the research agenda for GBS.

3. Listeriosis

KEY FACTS

- Listeriosis is a serious, but preventable and treatable disease.
- Pregnant women, the elderly or individuals with a weakened immune system, such as people with immuno-compromised status due to HIV, leukaemia, cancer, kidney transplant and steroid therapy, are at greatest risk of severe listeriosis and should avoid high risk foods.
- High risk foods include deli meat and ready-to-eat meat products (such as cooked, cured and/or fermented meats and sausages), soft cheeses and cold smoked fishery products.
- Listeria monocytogenes are widely distributed in nature. They can be found in soil, water, vegetation and the faeces of some animals and can contaminate foods.
- Listeriosis is an infectious disease caused by the bacterium Listeria monocytogenes.

Foodborne listeriosis is one of the most serious and severe foodborne diseases. It is caused by the bacteria *Listeria monocytogenes*. It is a relatively rare disease with 0.1 to 10 cases per 1 million people per year depending on the countries and regions of the world. Although the number of cases of listeriosis is small, the high rate of death associated with this infection makes it a significant public health concern.

Unlike many other common foodborne diseases causing bacteria, *L. monocytogenes*can survive and multiply at low temperatures usually found in refrigerators. Eating contaminated food with high numbers of *L. monocytogenes* is the main route of infection. Infection can also be transmitted between humans, notably from pregnant women to unborn babies.

L. monocytogenes are ubiquitous in nature and found in soil, water and animal digestive tracts. Vegetables may be contaminated through soil or the use of manure as fertilizer. Ready-to-eat food can also become contaminated during processing and the bacteria can multiply to dangerous levels during distribution and storage.

Food most often associated with listeriosis include:

- foods with a long shelf-life under refrigeration (*L. monocytogenes* can grow to significant numbers in food at refrigeration temperatures when given sufficient time); and
- foods that are consumed without further treatment, such as cooking, which would otherwise kill *L. monocytogenes*.

In past outbreaks, foods involved included ready-to-eat meat products, such as frankfurters, meat

spread (paté), smoked salmon and fermented raw meat sausages, as well as dairy products (including soft cheeses, unpasteurized milk and ice cream) and prepared salads (including coleslaw and bean sprouts) as well as fresh vegetables and fruits.

The disease

Listeriosis is a series of diseases caused by the bacteria *L. monocytogenes*, outbreaks of which occur in all countries. There are two main types of listeriosis: a non-invasive form and an invasive form.

Noninvasive listeriosis (febrile listerial gastroenteritis) is a mild form of the disease affecting mainly otherwise healthy people. Symptoms include diarrhoea, fever, headache and myalgia (muscle pain). The incubation period is short (a few days). Outbreaks of this disease have generally involved the ingestion of foods containing high doses of *L. monocytogenes*.

Invasive listeriosis is a more severe form of the disease and affects certain high risk groups of the population. These include pregnant women, patients undergoing treatment for cancer, HIV and organ transplants, elderly people and infants. This form of disease is characterized by severe symptoms and a high mortality rate (20–30%). The symptoms include fever, myalgia (muscle pain), septicemia, meningitis. The incubation period is usually one to two weeks but can vary between a few days and up to 90 days.

The initial diagnosis of listeriosis is made based on clinical symptoms and detection of the bacteria in a smear from blood, cerebrospinal fluid (CSF), meconium of newborns (or the fetus in abortion cases), as well as from faeces, vomitus, foods or animal feed. Various detection methods, including polymerase chain reaction (PCR), are available for diagnosis of listeriosis in humans. During pregnancy, blood and placenta cultures are the most reliable ways to discover if symptoms are due to listeriosis.

Pregnant women are about 20 times more likely to contract listeriosis than other healthy adults. It can result in miscarriage or stillbirth. Newborn may also have low birth weight, septicaemia and meningitis. People with HIV are at least 300 times more likely to get ill than those with a normally functioning immune system.

Due to the long incubation period, it is challenging to identify the food which was the actual source of the infection.

Treatment

Listeriosis can be treated if diagnosed early. Antibiotics are used to treat severe symptoms such as meningitis. When infection occurs during pregnancy, prompt administration of antibiotics prevents infection of the fetus or newborn.

Control methods

The control of *L. monocytogenes* is required at all stages in the food chain and an integrated approach is needed to prevent the multiplication of this bacteria in the final food product. The challenges for controlling *L. monocytogenes* are considerable given its ubiquitous nature, high resistance to common preservative methods, such as the use of salt, smoke or acidic condition in the food, and its ability to survive and grow at refrigeration temperatures (around 5 °C). All sectors of the food chain should Implement Good Hygienic Practices (GHP) and Good Manufacturing Practices (GMP) as well as implement a food safety management system based on the principles of Hazard Analysis Critical Control Points (HACCP).

Food manufacturers should also test against microbiological criteria, as appropriate, when validating and verifying the correct functioning of their HACCP based procedures and other hygiene control measures. In addition, producers manufacturing food associated with risks of Listeria must conduct environmental monitoring to identify and eliminate niche environments, including areas that favor the establishment and proliferation of *L. monocytogenes*.

Modern technologies using genetic fingerprint – Whole Genome Sequencing (WGS) – allow for more rapid identification of the food source of listeriosis outbreaks by linking *L. monocytogens* isolated from patients with those isolated from foods.

Prevention

L. monocytogenes in food are killed by pasteurization and cooking. In general, guidance on the prevention of listeriosis is similar to guidance used to help prevent other foodborne illnesses. This includes practicing safe food handling and following the WHO Five Keys to Safer Food:

1. Keep clean
2. Separate raw and cooked
3. Cook thoroughly
4. Keep food at safe temperatures
5. Use safe water and raw materials.

- Poster: Five Keys to Safer Food

Persons in high risk groups should:

- Avoid consuming dairy products made of unpasteurized milk; deli meats and ready-to-eat meat products such as sausages, hams, patés and meat spreads, as well as cold-smoked seafood (such as smoked salmon);
- Read and carefully follow the shelf life period and storage temperatures indicated on the product label.

It is important to respect the shelf-life and storage temperature written on labels of ready-to-eat foods to ensure that bacteria potentially present in these

foods does not multiply to dangerously high numbers. Cooking before eating is another very effective way to kill the bacteria.

WHO response

WHO promotes the strengthening of food safety systems, good manufacturing practices and educating retailers and consumers on appropriate food handling and avoiding contamination. Educating consumers, especially those in high risk groups, and training of food handlers in safe food handling are among the most critical means to prevent foodborne illnesses including listeriosis.

WHO and FAO have published an international quantitative risk assessment of Listeria in ready-to-eat foods This has formed the scientific basis for the Codex Alimentarius Commission *Guidelines on the Application of General Principles of Food Hygiene to the Control of Listeria Monocytogenes in Foods*. This guidance includes microbiological criteria (i.e. maximum limits for the presence of *L. monocytogenes* in foods)

WHO's main tool to assist Member States in surveillance, coordination and response to outbreaks is the International Network of Food Safety Authorities (INFOSAN) which links national authorities in Member States in charge of managing food safety events. This network is managed jointly by WHO and FAO.

4. Natural toxins in food

KEY FACTS

- Some natural toxins can be formed in food as defense mechanisms of plants, through their infestation with toxin-producing mould, or through ingestion by animals of toxin-producing microorganisms.
- Natural toxins can cause a variety of adverse health effects and pose a serious health threat to both humans and livestock. Some of these toxins are extremely potent.
- Adverse health effects can be acute poisoning ranging from allergic reactions to severe stomachache and diarrhoea, and even death.
- Long-term health consequences include effects on the immune, reproductive or nervous systems, and also cancer.
- A scientific expert committee jointly convened by WHO and the Food and Agriculture Organization of the United Nations (FAO) – called JECFA – is the international body responsible for evaluating the health risk from natural toxins in food.
- International standards and codes of practice to limit exposure to natural toxins from certain foods are established by the Codex Alimentarius Commission based on JECFA assessments.

What are natural toxins?

Natural toxins are toxic compounds that are naturally produced by living organisms. These toxins are not harmful to the organisms themselves but they may be toxic to other creatures, including humans, when eaten. These chemical compounds have diverse structures and differ in biological function and toxicity.

Some toxins are produced by plants as a natural defense mechanism against predators, insects or microorganisms, or as consequence of infestation with microorganisms, such as mould, in response to climate stress (such as drought or extreme humidity).

Other sources of natural toxins are microscopic algae and plankton in oceans or sometimes in lakes that produce chemical compounds that are toxic to humans but not to fish or shellfish that eat these toxin-producing organisms. When people eat fish or shellfish that contain these toxins, illness can rapidly follow.

Some of the most commonly found natural toxins that can pose a risk to our health are described below.

Aquatic biotoxins

Toxins formed by algae in the ocean and fresh water are called algal toxins. Algal toxins are generated during blooms of particular naturally occurring algal species. Shellfish such as mussels, scallops and oysters are more likely to contain these toxins than fish. Algal toxins can cause diarrhea, vomiting, tingling, paralysis and other effects in humans, other mammals or fish. The algal toxins can be retained in shellfish and fish or contaminate drinking water. They have no taste or smell, and are not eliminated by cooking or freezing.

Another example is ciguatera fish poisoning (CFP) which is caused by consuming fish contaminated with dinoflagellates that produce ciguatoxins. Some fish known to harbour ciguatoxins include barracuda, black grouper, dog snapper, and king mackerel. Symptoms of ciguatera poisoning include nausea, vomiting, and neurologic symptoms, such as tingling sensation on fingers and toes. There is currently no specific treatment for ciguatera poisoning.

Cyanogenic glycosides

Cyanogenic glycosides are phytotoxins (toxic chemicals produced by plants) which occur in at least 2000 plant species, of which a number of species are used as food in some areas of the world. Cassava, sorghum, stone fruits, bamboo roots and almonds are especially important foods containing cyanogenic glycosides. The potential toxicity of a cyanogenic plant depends primarily on the potential that its consumption will produce a concentration of cyanide that is toxic to exposed humans. In humans, the clinical signs of acute cyanide intoxication can include: rapid respiration, drop in blood pressure, dizziness,

headache, stomach pains, vomiting, diarrhoea, mental confusion, cyanosis with twitching and convulsions followed by terminal coma. Death due to cyanide poisoning can occur when the cyanide level exceeds the limit an individual is able to detoxify.

Furocoumarins

These toxins are present in many plants such as parsnips (closely related to carrots and parsley), celery roots, citrus plants (lemon, lime, grapefruit, bergamot) and some medicinal plants. Furocoumarins are stress toxins and are released in response to stress, such as physical damage to the plant. Some of these toxins can cause gastrointestinal problems in susceptible people. Furocoumarins are phototoxic, they can cause severe skin reactions under sunlight (UVA exposure). While mainly occurring after dermal exposure, such reactions have also been reported after consumption of large quantities of certain vegetables containing high levels of furocoumarins.

Lectins

Many types of beans contain toxins called lectins, and kidney beans have the highest concentrations – especially red kidney beans. As few as 4 or 5 raw beans can cause severe stomachache, vomiting and diarrhoea. Lectins are destroyed when the dried beans are soaked for at least 12 hours and then boiled vigorously for at least 10 minutes in water. Tinned kidney beans have already had this process applied and so can be used without further treatment.

Mycotoxins

Mycotoxins are naturally occurring toxic compounds produced by certain types of moulds. Moulds that can produce mycotoxins grow on numerous foodstuffs such as cereals, dried fruits, nuts and spices. Mould growth can occur before harvest or after harvest, during storage, on/in the food itself often under warm, damp and humid conditions.

Most mycotoxins are chemically stable and survive food processing. The effects of food-borne mycotoxins can be acute with symptoms of severe illness and even death appearing quickly after consumption of highly contaminated food products. Long term effects on health of chronic mycotoxin exposure include the induction of cancers and immune deficiency.

Solanines and chaconine

All solanacea plants, which include tomatoes, potatoes, and eggplants, contain natural toxins called solanines and chaconine (which are glycoalkaloids). While levels are generally low, higher concentrations are found in potato sprouts and bitter-tasting peel and green parts, as well as in green tomatoes. The plants produce the toxins in response to stresses like bruising, UV light, microorganisms and attacks from insect pests and herbivores. To reduce the production of solanines and chaconine it is important to store potatoes in a dark, cool and dry place, and not to eat green or sprouting parts.

Poisonous mushrooms

Wild mushrooms may contain several toxins, such as muscimol and muscarine, which can cause vomiting, diarrhoea, confusion, visual disturbances, salivation, and hallucinations. Onset of symptoms occurs 6–24 hours or more after ingestion of mushrooms. Fatal poisoning is usually associated with delayed onset of symptoms which are very severe, with toxic effect on the liver, kidney and nervous systems. Cooking or peeling does not inactivate the toxins. It is recommended to avoid any wild mushrooms, unless definitively identified as non-poisonous.

Pyrrolizidine alkaloids

Pyrrolizidine Alkaloids (PAs) are toxins produced by an estimated 600 plant species. The main plant sources are the families *Boraginaceae*, *Asteraceae* and *Fabaceae*. Many of these are weeds that can grow in fields and contaminate food crops. PAs can cause a variety of adverse health effects; they can be acutely toxic and of main concern is the DNA-damaging potential of certain PAs, potentially leading to cancer. PAs are stable during processing, and have been detected in herbal teas, honey, herbs and spices and other food products, such as cereals and cereal products. Human exposure is estimated to be low, however. Due to the complexity of the subject and the large number of related compounds, the overall health risk has not been fully evaluated yet. Guidance is under development by the FAO/WHO Codex Committee on Contaminants in Food on management strategies to prevent PA-containing plants from entering the food chain.

How can I minimize the health risk from natural toxins?

When it comes to natural toxins it is important to note that they can be present in a variety of different crops and foodstuff. In a usual balanced, healthy diet, the levels of natural toxins are well below the threshold for acute and chronic toxicity.

To minimize the health risk from natural toxins in food, people are advised to:

- not assume that if something is 'natural' it is automatically safe;
- throw away bruised, damaged or discoloured food, and in particular mouldy foods;
- throw away any food that does not smell or taste fresh, or has an unusual taste; and

- only eat mushrooms or other wild plants that have definitively been identified as nonpoisonous.

WHO response

WHO, in collaboration with FAO, is responsible for assessing the risks to humans of natural toxins – through contamination in food – and for recommending adequate protections.

Risk assessments of natural toxins in food done by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) are used by governments and by the Codex Alimentarius Commission (the intergovernmental standards-setting body for food) to establish maximum levels in food or provide other risk management advice to control or prevent contamination. Codex standards are the international reference for national food supplies and for trade in food, so that people everywhere can be confident that the food they buy meets the agreed standards for safety and quality, no matter where it was produced.

JECFA or ad hoc FAO/WHO scientific expert groups consist of independent, international experts who conduct scientific reviews of all available studies and other relevant data on specific natural toxins. The outcome of such health risk assessments can either be a maximum tolerable intake (exposure) level, or other guidance to indicate the level of health concern (such as the Margin of Exposure), including advice on risk management measures to prevent and control contamination, and on the analytical methods and monitoring and control activities.

Exposure to natural toxins needs to be kept as low as possible to protect people. Natural toxins not only pose a risk to both human and animal health, but also impact food security and nutrition by reducing people's access to healthy food. WHO encourages national authorities to monitor and ensure that levels of the most relevant natural toxins in their food supply are as low as possible and comply with both national and international maximum levels, conditions and legislation.

5. Sepsis

KEY FACTS

- Sepsis is a syndromic response to infection and is frequently a final common pathway to death from many infectious diseases worldwide
- The global burden of sepsis is difficult to ascertain, although a recent scientific publication estimated that in 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths (1)
- In 2017, almost half of all global sepsis cases occurred among children, with an estimated 20 million cases and 2.9 million global deaths in children under five years of age (1)
- Significant regional disparities in sepsis incidence and mortality exist; approximately 85.0% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries (1)
- Sepsis can be the clinical manifestation of infections acquired both in the community setting or in health care facilities. Health care-associated infections are one of, if not the most frequent type of adverse event to occur during care delivery and affect hundreds of millions of patients worldwide every year (2). Since these infections are often resistant to antibiotics, they can rapidly lead to deteriorating clinical conditions.

Background

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection (3). If not recognized early and managed promptly, it can lead to septic shock, multiple organ failure and death. It is most frequently a serious complication of infection, particularly in low- and middle-income countries where it represents a major cause of maternal and neonatal morbidity and mortality.

In the community setting, sepsis often presents as the clinical deterioration of common and preventable infections. Sepsis also frequently results from infections acquired in health care settings, which are one of the most frequent adverse events during care delivery and affect hundreds of millions of patients worldwide every year (2).

Healthcare-associated infections are often resistant to antibiotics and can rapidly lead to deteriorating clinical conditions. Antimicrobial resistance is a major factor determining clinical unresponsiveness to treatment and rapid evolution to sepsis and septic shock. Sepsis patients with resistant pathogens have been found to have a higher risk of hospital mortality.

Implementing preventive measures against infections, such as good hygiene practices, ensuring access to vaccination programmes, improved sanitation and water quality and availability, and other infection prevention and control best practices both in the community and health care settings, are key steps in reducing the occurrence of sepsis. Early diagnosis and timely and appropriate clinical management of sepsis, such as optimal antimicrobial use and fluid resuscitation, are crucial to increase the likelihood of survival. Even though the onset of sepsis can be acute and poses a short-term mortality burden, it can also be the cause of significant long-term morbidity requiring treatment and support. Thus, sepsis requires a multidisciplinary approach.

Who is at risk?

Anyone affected by an infection, severe injury, or serious non-communicable disease can progress to sepsis but vulnerable populations are at higher risk (4) including:

- older persons,
- pregnant or recently pregnant women,
- neonates,
- hospitalized patients,
- patients in intensive care units,
- people with HIV,
- people with liver cirrhosis,
- people with cancer,
- people with kidney disease,
- people with autoimmune diseases,
- and people with no spleen.

Signs and symptoms

Sepsis is a medical emergency and can present with various signs and symptoms at different times. Warning signs and symptoms include:

- fever or low temperature and shivering,
- altered mental status,
- difficulty breathing/rapid breathing,
- increased heart rate,
- weak pulse/low blood pressure,
- low urine output,
- cyanotic or mottled skin,
- cold extremities,
- and extreme body pain or discomfort (5-7).

Suspecting sepsis is a first major step towards early recognition and diagnosis.

Common Causes

In 2017, the largest contributors to sepsis cases and sepsis-related mortality across all ages were diarrhoeal diseases (9.2 to 15 million annual cases) and lower respiratory infections (1.8-2.8 million annually) (1). However, non-communicable diseases are on the rise; one-third of sepsis cases and nearly half of all sepsis-related deaths in 2017 were due to an underlying injury or chronic disease (1). Maternal disorders were the most common non-communicable disease complicated by sepsis. Among children, the most common causes of sepsis-related deaths were neonatal disorders, lower respiratory infections, and diarrhoeal diseases (1). Group B streptococcus is the leading cause of both neonatal and maternal sepsis, though *Escherichia coli* is an emerging threat (8,9). Both of these pathogens have displayed considerable resistance to treatment and are considered priority pathogens for research and development (R&D) of new antibiotics.

Sepsis Prevention

There are two main steps to preventing sepsis:

1. Prevention of microbial transmission and infection
2. Prevention of an infection evolving into sepsis

Prevention of infection in the community involves using effective hygiene practices, such as hand washing, and safe preparation of food, improving sanitation and water quality and availability, providing access to vaccines, particularly for those at high risk, as well as appropriate nutrition, including breastfeeding for newborns.

Prevention of infection in health care facilities mainly relies on having functioning infection prevention and control (IPC) programmes and teams, effective hygiene practices and precautions, including hand hygiene, along with a clean, well-functioning environment and equipment.

Prevention of the evolution to sepsis in both community and health care facilities requires the appropriate antibiotic treatment of infection, including reassessment for optimization, prompt seeking of medical care, and early detection of sepsis signs and symptoms.

Diagnosis and Clinical Management

Identifying and not underestimating the signs and symptoms listed above, along with the detection of some biomarkers (such as C reactive protein and procalcitonin), are crucial elements for early diagnosis of sepsis and the timely establishment of its appropriate clinical management. After early recognition, diagnostics to help identify a causal pathogen of infection leading to sepsis are important to guide targeted antimicrobial treatment. Once the source of infection is determined, source control, such as drainage of an abscess, is critical. Antimicrobial resistance (AMR) can jeopardize clinical management of sepsis because empirical antibiotic treatment is often required. Early fluid resuscitation to improve volume status is also important in the initial phase of sepsis management. In addition, vasopressors may be required to improve and maintain tissue perfusion. Repeated exams and assessments, including monitoring vital signs, guide the appropriate management of sepsis over time.

Sepsis and the Sustainable Development Goals

Sepsis is a significant cause of maternal, neonatal and child mortality. Consequently, combating sepsis will contribute to achievement of Sustainable Development Goals (SDGs) targets 3.8 on quality of care, and 3.1 and 3.2 by improving mortality rates in these vulnerable populations. Sepsis can also ultimately lead to death in patients affected by HIV, tuberculosis, malaria, and other infectious diseases that are included in target

3.3. The prevention and/or appropriate diagnosis and management of sepsis is also linked to adequate vaccine coverage, quality universal health coverage, capacity to comply with the International Health Regulations, preparedness, and water and sanitation services. The challenge, however, remains how to achieve universal prevention, diagnosis and management of sepsis.

WHO Sepsis Response

To combat this important global health threat, WHO responded with a WHO Secretariat Report and, in May 2017, the Seventieth World Health Assembly adopted Resolution WHA70.7 on *Improving the prevention, diagnosis and clinical management of sepsis*. The key pillars of Resolution WHA 70.7 are to:

1. Develop WHO guidance on sepsis prevention and management
2. Draw attention to public health impacts of sepsis and estimate the global burden of sepsis
3. Support Member States to define and implement standards and establish guidelines, infrastructure, laboratory capacity, strategies, and tools for identifying, reducing incidence of, and morbidity and mortality due to sepsis
4. Collaborate with UN organizations, partners, international organizations, and stakeholders to enhance sepsis treatment and infection prevention and control including vaccinations

In collaboration and coordination with WHO regional offices, Member States and other stakeholders, several WHO headquarters programmes are currently working on the public health impact of sepsis and providing guidance and country support on sepsis prevention, early and appropriate diagnosis, and timely and appropriate clinical management.

REFERENCES

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet (London, England). 2020;395(10219):200-11.
2. World Health Organization. WHO Report on the burden of endemic health care-associated infection worldwide. 2017-11-21 15:11:22 2011.
3. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8): 801-10.
4. Gotts JE, Matthay MA. Sepsis: pathophysiology and clinical management. British Medical Journal 2016.
5. United States Centers for Disease Control and Prevention. Healthcare Professional (HCP) Resources : Sepsis. Updated August 27, 2019. T06:23:15Z. https://www.cdc.gov/sepsis/get-ahead-of-sepsis/hcp-resources.html (accessed 25 February 2020).
6. Global Sepsis Alliance. Toolkits. https://www.world-sepsis-day.org/toolkits/ (accessed 25 February 2020).
7. UK Sepsis Trust. Education. 2018. https://sepsistrust.org/education/ (accessed 25 February 2020).
8. Lawn JE, Bianchi-Jassir F, Russell NJ, Kohli-Lynch M, Tann CJ, Hall J, et al. Group B Streptococcal Disease Worldwide for Pregnant Women, Stillbirths, and Children: Why, What, and How to Undertake Estimates? Clin Infect Dis. 2017;65(suppl_2):S89-S99.
9. Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. Pediatrics. 2011;127(5):817-26.