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Meta-Analysis

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Transthoracic *vs.* transesophageal echocardiography in transcatheter aortic valve implantation: a systematic review and meta-analysis

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Abstract

Aim: Traditionally, transcatheter aortic valve implantation (TAVI) was performed under general anesthesia (GA) accompanied by intraprocedural transesophageal echocardiography (TEE). Recently, minimalist TAVI with monitored anesthesia care (MAC) and transthoracic echocardiography (TTE) has gained popularity. However, TTE imaging quality may be suboptimal compared to TEE and may increase the risks of paravalvular leak (PVL). We sought to compare TTE to TEE for PVL (primary outcome) and secondary safety outcomes in a study-level meta-analysis.

Methods: Ovid versions of Medline and Embase were searched from 1946 to 2018 for studies comparing TTE to TEE in TAVI directly or MAC to GA in TAVI (must also specify echocardiography usage) and meta-analyzed in a random effects model.

Results: Sixteen studies (n = 3,510) were included in the meta-analysis. The rate of any PVL was not significantly different between TTE-TAVI and TEE-TAVI groups (18.4% *vs.* 21.4%, risk ratio: 1.01, 95%CI: 0.83 to 1.23, P = 0.92, I^2 = 36%). Similarly, there were no significant differences in secondary safety outcomes. Resource utilization was lower with TTE-TAVI; hospital LOS [mean difference (MD): -1.55 days, 95%CI: -2.27 to -0.83, P < 0.01], contrast volume (MD: -24.75 mL, 95%CI: -49.48 to -0.03, P = 0.05) and procedure time (MD: -31.09 min, 95%CI: -54.77 to -7.40, P < 0.01) were significantly lower.

Conclusion: The use of TTE-TAVI in conjunction with MAC was not associated with an increased risk of PVL and was associated with lower hospital resource utilization. However, other factors, such as mode of anesthesia, may have influenced these findings.

Keywords: Transcatheter aortic valve implantation, transthoracic echocardiography, transesophageal echocardiography

INTRODUCTION

The volume of transcatheter aortic valve implantation (TAVI) has surpassed surgical aortic valve replacement in Europe and North America[1-3]. Traditionally, TAVI uses general anesthesia (GA) accompanied by intraprocedural transesophageal echocardiography (TEE) to assess root geometry and guide valve placement during the procedure[4]. While rare, TEE can also lead to serious complications such as esophageal perforation, aspiration and oropharyngeal damage[5].

Recently, minimalist TAVI conducted under monitored anesthesia care (MAC) has gained popularity. Studies suggest that it is less invasive and allows for earlier mobilization and patient discharge without compromising early outcomes[6]. Since TEE is not usually conducted under MAC, minimalist TAVI often uses transthoracic echocardiography (TTE) instead[5]. Image quality with TTE may be suboptimal compared to TEE and may have a lower sensitivity in detecting paravalvular leaks (PVL)[5,7-8]. Studies have shown that PVL after TAVI is often poorly tolerated and associated with excess late mortality[8,9]. Thus, understanding whether PVL increases in patients undergoing TAVI with TTE compared to TEE is paramount. There are few studies directly comparing TTE and TEE in TAVI and the sample size in these studies are limited. However, there are many studies that compare usage of MAC and GA in TAVI[6]. Since TTE and TEE usage is closely associated with the mode of anesthesia, MAC and GA can be used as surrogate variables for TTE and TEE respectively.

This quantitative meta-analysis aims to compare early echocardiography parameters and safety outcomes in TTE-TAVI and TEE-TAVI. The primary outcome is PVL and secondary outcomes include 30-day mortality, renal failure, stroke, major bleeds, hospital length of stay (LOS), ICU LOS, fluoroscopy time, contrast volume and procedure time.

METHODS

Systematic literature review

Ovid versions of Medline and Embase were searched from 1946 to June 18, 2018 for the following key terms: “Transcatheter aortic valve implantation,” “echocardiography” and “anesthesia”. The full search strategy is shown in Supplementary Appendix S1. Inclusion criteria included the following: English, comparison of TTE to TEE or MAC to GA in TAVI, reported at least 1 chosen outcome. MAC vs GA papers must also specify the frequency of TTE and TEE usage. Exclusion criteria included the following: non-English studies, conference abstracts, proceedings, case reports and other non-comparative study designs. The citations from the literature search were compared to papers in a meta-analysis comparing MAC to GA in TAVI to ensure papers were not missed[6].

All titles and abstracts were reviewed. Full papers of citations that could potentially be included in the study were further analyzed. The literature search results were reviewed independently by 2 investigators (T.L. and A.D.). Disagreements were discussed by investigators until an agreement was reached.

Quality assessment and data abstraction

Quality of studies were assessed with the Grading of Recommendations Assessment, Development and Evaluation approach[10]. The following outcomes were abstracted: usage of TTE, usage of TEE, mild PVL, moderate PVL, severe PVL, any PVL, 30-day mortality, renal failure, stroke, major bleeds, hospital LOS, ICU LOS, fluoroscopic time, contrast volume, and procedure time.

Analysis

A random effects meta-analysis was performed with R packages meta and metafor (R version 3.5.0; R Foundation for Statistical Computing, Vienna, Austria). If only the median and quartiles were provided in a study, mean and standard deviation were estimated based on protocol found in the literature[11,12]. Risk ratios (RRs) weighted based on number of events and sample size were calculated using the Mantel-Haenszel method for perioperative dichotomous outcomes. The event rates and percentages for all subgroups were calculated based on raw data for perioperative dichotomous outcomes. Mean differences (MD) were used to analyze continuous variables as calculated by the inverse variance method. Means were also calculated based on raw data for continuous variables. Heterogeneity was reported as low (I^2 = 0%-25%), moderate (I^2 = 26%-50%), or high (I^2 > 50%), as reported previously in the literature[13]. Data was analyzed as a pooled group then as 2 sub-groups: matched and unmatched observational studies.

One additional post hoc analysis was conducted. It compared studies that only used TTE in the MAC group to studies that had mixed TTE and TEE usage in the MAC group on the outcome of PVL.

RESULTS

After searching in Ovid and Embase, 1,133 citations were screened. Sixteen citations (*n* = 3510 patients) fulfilled the inclusion and exclusion criteria. There were 10 unmatched (*n* = 2037 patients)[7,14-22] and 6 matched (*n* = 1473 patients)[4,23-27] retrospective observational studies [Supplementary Figure 1].

The studies were rated at low or moderate risk of bias [Supplementary Table 1]. All studies had concurrent controls. Twelve studies[4,14-18,20,21,24-27] did not report follow up rates. One study lost more than 10% of patients in the 1 year follow-up[7]. TTE-TAVI and TEE-TAVI shared similar baseline characteristic, including predicted mortality risk scores [Supplementary Tables 2 and 3].

Primary outcome: PVL

Event rates and relative risks for the primary outcome and periprocedural events are summarized in Table 1. Corresponding forest plots are shown in Figure 1 and Supplementary Figures 2-8. The incidence rate in pooled results for mild PVL was not significantly different when TTE-TAVI was compared to TEE-TAVI (32.1% *vs.* 34.0%, RR: 0.95, 95%CI: 0.72 to 1.25, *P* = 0.71, I^2 = 54%). Similar non-significant results were found for moderate PVL (6.6% *vs.* 6.7%, RR: 0.87, 95%CI: 0.55 to 1.38, *P* = 0.56, I^2 = 0%), severe PVL (0.9% *vs.* 0.3%, RR: 1.39, 95%CI: 0.06 to 33.21, *P* = 0.84, I^2 = 53%), and any PVL ^{3} mild (18.4% *vs.* 21.4%, RR: 1.01, 95%CI: 0.83 to 1.23, *P* = 0.92, I^2 = 36%). All subgroups also did not show any significant difference between TTE-TAVI and TEE-TAVI.

Periprocedural events

When comparing patients that had TTE and TEE at the time of TAVI, there was no significant difference in pooled event rates for 30-day mortality (4.0% *vs.* 5.0%, RR: 0.69, 95%CI: 0.49 to 1.13, *P* = 0.14, I^2 = 0%) [Table 1]. Similarly, when TTE-TAVI was compared to TEE-TAVI, no significant differences were found for renal failure (5.4% *vs.* 4.0%, RR: 0.86, 95%CI: 0.58 to 1.26, *P* = 0.43, I^2 = 0%), stroke (2.8% *vs.* 2.7%, RR: 0.85, 95%CI: 0.52 to 1.39, *P* = 0.52, I^2 = 0%), and major bleed (2.8% *vs.* 5.1%, RR: 0.58, 95%CI: 0.28 to 1.22, *P* = 0.15, I^2 = 45%) [Table 1]. All subgroups also did not show a significant difference when TTE-TAVI was compared to TEE-TAVI.

Hospital resources

The weighted means and MDs for the continuous outcomes are summarized in Table 2. Corresponding forest plots are depicted in Figure 2 and Supplementary Figures 9-12. Hospital LOS was significantly

Table 1. Pooled event rates and relative risks for dichotomous events from meta-analysis

	TTE event rate	TEE event rate	RR (95%CI)	*P* value
Mild PVL				
Observational adjusted	33/93 (35.5%)	33/106 (31.1%)	1.09 (0.4 to 2.95)	0.87
Observational unadjusted	132/421 (31.4%)	158/456 (34.6%)	0.89 (0.73 to 1.08)	0.23
Pooled	165/514 (32.1%)	191/562 (34.0%)	0.95 (0.72 to 1.25)	0.71
Moderate PVL				
Observational adjusted	3/47 (6.4%)	0/64 (0.0%)	9.48 (0.5 to 179.24)	0.13
Observational unadjusted	32/482 (6.6%)	32/417 (7.7%)	0.82 (0.52 to 1.31)	0.41
Pooled	35/529 (6.6%)	32/481 (6.7%)	0.87 (0.55 to 1.38)	0.56
Severe PVL				
Observational adjusted	3/350 (0.9%)	1/311 (0.3%)	1.39 (0.06 to 33.21)	0.84
Observational unadjusted				N/A
Pooled	3/350 (0.9%)	1/311 (0.3%)	1.39 (0.06 to 33.21)	0.84
Any PVL				
Observational adjusted	118/710 (16.6%)	95/675 (14.1%)	1.34 (0.81 to 2.22)	0.25
Observational unadjusted	189/954 (19.8%)	199/698 (28.5%)	0.89 (0.76 to 1.05)	0.16
Pooled	307/1,664 (18.4%)	294/1,373 (21.4%)	1.01 (0.83 to 1.23)	0.92
30-day mortality				
Observational adjusted	5/90 (5.6%)	5/86 (5.8%)	0.96 (0.28 to 3.27)	0.94
Observational unadjusted	37/955 (3.9%)	31/628 (4.9%)	0.65 (0.37 to 1.11)	0.11
Pooled	42/1,045 (4.0%)	36/714 (5.0%)	0.69 (0.49 to 1.13)	0.14
Renal Failure				
Observational adjusted	20/707 (2.8%)	10/655 (1.5%)	1.42 (0.57 to 3.55)	0.45
Observational unadjusted	59/760 (7.8%)	36/486 (7.4%)	1.61 (0.34 to 7.7)	0.18
Pooled	79/1,467 (5.4%)	46/1,141 (4.0%)	0.86 (0.58 to 1.26)	0.43
Stroke				
Observational adjusted	15/614 (2.4%)	15/627 (2.4%)	1.01 (0.49 to 2.07)	0.99
Observational unadjusted	26/834 (3.1%)	17/555 (3.1%)	0.73 (0.37 to 1.44)	0.36
Pooled	41/1,448 (2.8%)	32/1,182 (2.7%)	0.85 (0.52 to 1.39)	0.52
Major bleed				
Observational adjusted	23/567 (4.1%)	39/563 (6.9%)	0.48 (0.13 to 1.7)	0.25
Observational unadjusted	12/689 (1.7%)	9/382 (2.4%)	0.79 (0.31 to 2.05)	0.63
Pooled	35/1,256 (2.8%)	48/945 (5.1%)	0.58 (0.28 to 1.22)	0.15

Rate of characteristics are depicted as crude counts and percentages. Using the Mantel-Haenszel method, the weighted RR ratios were calculated. TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; RR: relative risk; CI: confidence interval; PVL: paravalvular leak

shorter in the TTE-TAVI group compared to the TEE-TAVI group (MD: -1.55 days, 95%CI: -2.27 to -0.83, $P \leq 0.01$). However, hospital LOS was significantly lower in unmatched observational studies (MD: -1.89 days, 95%CI: -2.6 to -1.17, $P \leq 0.01$) but equivalent in matched observational studies (MD: -0.91 days, 95%CI: -2.27 to 0.44, $P = 0.19$).

ICU LOS was not significantly different in the TTE group in comparison to the TEE group (MD: -5.6 h, 95%CI: -13.66 to 2.45, $P = 0.17$). ICU LOS was significantly lower in unmatched observational studies (MD: -12.68 h, 95%CI: -22.28 to -3.09, $P \leq 0.01$) but equivalent in matched observational studies (MD: 6.22 h, 95%CI: -16.34 to 28.78, $P = 0.59$).

Fluoroscopic time was not significantly different in pooled results when TTE-TAVI was compared to TEE-TAVI (MD: -1.34 min, 95%CI: -2.84 to 0.16, $P = 0.08$). Likewise, fluoroscopic time was significantly reduced in unmatched observational studies (MD: -1.79 min, 95%CI: -3.36 to -0.22, $P = 0.03$) but equivalent in matched observational studies (MD: -0.71 min, 95%CI: 3.91 to 2.5, $P = 0.67$).

Analysis of the data showed that contrast volume was significantly higher in the TTE group (MD: -24.75 mL, 95%CI: -49.48 to -0.03, $P = 0.05$). However, this trend was driven by the matched observational subgroup,

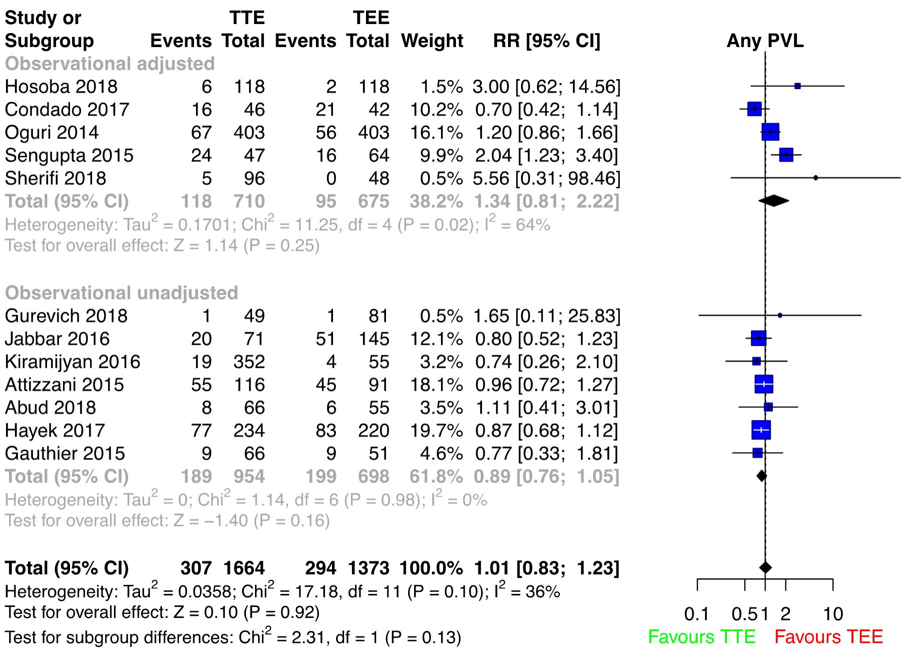

Figure 1. Forest plot for relative risk ratios of any PVL for TTE-TAVI in comparison to TEE-TAVI with subgroups based on study type. TTE; transthoracic echocardiography; TEE: transesophageal echocardiography; RR: relative risk; CI: confidence interval; PVL: paravalvular leak; TAVI: transcatheter aortic valve implantation

Table 2. Pooled event means and weighted differences for continuous events from meta-analysis

	TTE mean	TEE mean	MD (95%CI)	*P* value
Length of stay (days)				
Observational adjusted	6.3	7.2	-0.91 (-2.27 to 0.44)	0.19
Observational unadjusted	5.3	7.2	-1.89 (-2.6 to -1.17)	< 0.01
Pooled	5.6	7.2	-1.55 (-2.27 to -0.83)	< 0.01
ICU time (h)				
Observational adjusted	59.7	54.2	6.22 (-16.34 to 28.78)	0.59
Observational unadjusted	39.6	59.5	-12.68 (-22.28 to -3.09)	< 0.01
Pooled	47.4	49.9	-5.6 (-13.66 to 2.45)	0.17
Fluoroscopic time (min)				
Observational adjusted	20.9	21.7	-0.71 (3.91 to 2.5)	0.67
Observational unadjusted	21.0	22.8	-1.79 (-3.36 to -0.22)	0.03
Pooled	21.0	22.3	-1.34 (-2.84 to 0.16)	0.08
Contrast volume (mL)				
Observational adjusted	126.7	161.7	-35.0 (-56.89 to -13.11)	< 0.01
Observational unadjusted	96.2	119.0	-22.83 (-51.14 to 5.48)	0.11
Pooled	101.2	126.0	-24.75 (-49.48 to -0.03)	0.05
Procedure time (min)				
Observational adjusted	98.6	118.1	-44.29 (-90.96 to 2.38)	< 0.06
Observational unadjusted	123.1	142.6	-19.44 (-33.01 to -5.87)	< 0.01
Pooled	110.5	130	-31.09 (-54.77 to -7.40)	0.01

TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; MD: mean difference; CI: confidence interval

which was significant (MD: -35.00 mL, 95%CI: -56.89 to -13.11, $P \leq 0.01$), and not significant in the unmatched observational subgroup (MD: -22.83 mL, 95%CI: -51.14 to 5.48, $P = 0.11$).

The procedure time was significantly shorter in the TTE group compared to the TEE group (MD: -31.09 min, 95%CI: -54.77 to -7.40, $P \leq 0.01$). The subgroups also showed similar patterns.

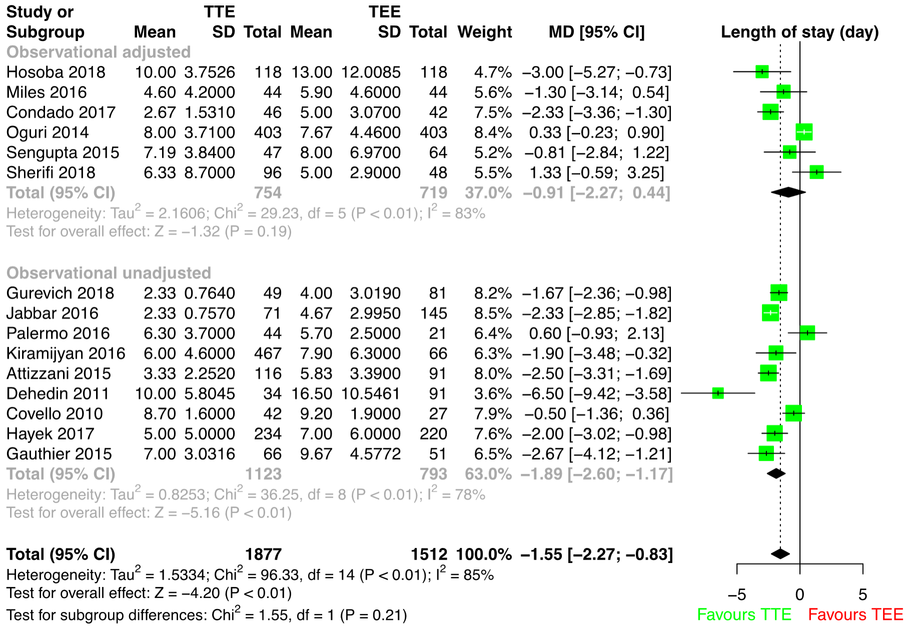

Figure 2. Forest plot for weighted mean differences (days) of length of stay for TTE-TAVI in comparison to TEE-TAVI with subgroups based on study type. TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; MD: mean difference; CI: confidence interval; TAVI: transcatheter aortic valve implantation

Post hoc analyses

Any PVL rates between TTE-TAVI and TEE-TAVI were compared in a subgroup analysis of MAC groups that only used TTE *vs.* MAC groups that had mixed TTE and TEE usage. There were 909 patients in the 100% TTE group and 755 patients in the mixed group. In the mixed echocardiography usage group, the mean use of TTE in the TAVI with MAC group was 50.0%. There were similar crude rates of PVL between the 100% TTE group compared to the mixed echocardiography usage group (18.4% *vs.* 21.4%). There were no significant differences of PVL between the 100% TTE group (RR: 1.00, 95%CI: 0.79 to 1.26, P = 0.98) and mixed echocardiography group (RR: 1.15, 95%CI: 0.84 to 1.57, P = 0.39, interaction P = 0.49) [Supplementary Figure 13].

DISCUSSION

This is the first meta-analysis using method of anesthesia to infer TTE and TEE status in conjunction with papers that directly compare TTE-TAVI with MAC and TEE-TAVI with GA. The rate of any PVL was not significantly different between TTE-TAVI with MAC and TEE-TAVI with GA. There was also no significant difference found for mild, moderate and severe PVL between the two groups. Importantly, there were no significant differences in safety outcomes such as 30-day mortality and complication rates. Resource utilization was lower with TTE use in conjunction with MAC; hospital LOS, contrast volume and procedure time were reduced. These results are important because the acute nature of post-TAVI PVL is poorly tolerated by patients; even mild PVL leads to higher early and late mortality[9,28]. Existing post-TAVI PVL treatments have not been widely validated[9]. For this reason, prophylactic measures to prevent PVL is paramount to safe TAVI procedures.

Of the 16 papers included in this meta-analysis, only 2 directly compared TTE and TEE[7,27]. Our meta-analysis narrowed the gap in the literature by using a surrogate variable, which enabled us to use an additional 5 matched and 9 unmatched observational studies for a total of 3150 patients. Similar to the previous 2 studies investigating echocardiography in TAVI, the Hayek *et al.*[7] and Sherifi *et al.*[27] (propensity matched) papers did not find significant differences in PVL complications between TTE-TAVI and TEE-TAVI groups[7,27]. However, this meta-analysis provides additional insight because it combines all available studies on this topic, allowing us to increase the sample size and power to examine for any differences.

Since TTE-TAVI with MAC was associated with shorter hospital LOS and procedure time, TTE-TAVI with MAC appeared to utilize less hospital resources without any increase in peri-operative morbidity and mortality. However, other factors may affect cost of procedure. Hayek *et al.*[7] found that TTE-TAVI was associated with significantly higher rates of second valve implantations (odds ratio = 1.58, 95%CI: 1.01 to 2.46), which may negate the beneficial effects of shorter LOS and procedure time on cost. Hence, a more detailed cost analysis will need to be conducted to determine the economic benefits of anesthesia and echocardiography type at the time of TAVI.

Limitations

This meta-analysis should be interpreted in the context of its limitations. While this is the largest meta-analysis to date to compare TTE to TEE for any PVL, we recognize that the sample size is still limited. Thus, our sample sizes for examining the outcomes of PVL grade may be underpowered to detect differences in outcomes. Only observational studies were found in the literature after a systematic literature review. Although there were no significant differences in baseline characteristics, including surgical risk scores, observational studies inherently include a risk of confounding variables. For example, PVL is influenced by many factors such as the type of prosthesis used, differences in procedural technique and center experience[29]. However, mode of anesthesia is the most concerning confounding variable. We acknowledge that differences in resource utilization may be the result of using MAC rather than substituting TTE for TEE alone. It is difficult to separate effects of anesthesia from the type of echocardiography as often the mode of anesthesia influences the choice of echocardiography performed. Furthermore, this study only analyzed early outcomes but did not assess late outcomes. Randomized clinical trials are needed to further investigate differences between TTE and TEE in TAVI.

In summary, the use of TTE-TAVI with MAC does not appear to adversely increase PVL rates compared to TEE-TAVI with GA. Furthermore, early mortality was similar between the two imaging modalities while resource utilization appeared to be lower with TTE, although this may have been associated with other factors such as mode of anesthesia.

DECLARATIONS

Authors' contributions

Data collection: Lam TK, Dixit AR
Data analysis/interpretation, drafting article: Lam TK
Approval of article: Lam TK, Tam DY, Dixit AR, Fremes SE
Concept/design: Tam DY, Fremes SE
Critical revision of article: Tam DY, Dixit AR, Fremes SE

Availability of data materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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