Repeat Thoracentesis in Hepatic Hydrothorax and Non-Hepatic Hydrothorax Effusions: A Case-Control Study

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Keywords

Complications · Repeat thoracentesis · Pleural effusion · Hepatic hydrothorax · Liver disease · Cirrhosis

Abstract

Background: Repeat thoracentesis for symptom control is offered to patients with refractory hepatic hydrothorax (HH) but the risk profile for this management strategy remains unclear. **Objectives:** This study aimed to compare complication frequency and nature during repeat thoracentesis in patients with and without HH. **Methods:** Complication rates in patients undergoing repeat thoracentesis for symptom relief was compared between patients with HH and a control group (non-HH group) at a single center from 2010 to 2015. Records were reviewed for demographics, laboratory values, number of thoracentesis, and associated complications with each procedure. **Results:** 82 patients with HH (274 thoracenteses) and 100 control patients (188 thoracenteses) were included. A complication was noted in 17/462 (0.03%) procedures in the entire cohort. There was a higher overall com-

plication rate with repeat thoracentesis in the HH group (8 vs. 0%, $p = 0.016$, 95% CI = 1.5–14.6). In the HH group, the cumulative risk of complications increased with sequential thoracenteses; a complication occurring in the preceding intervention was the strongest predictor for subsequent complication (OR = 17.1, $p = 0.0013$) and more than 1 previous complication was associated with a 15-fold increased risk of a subsequent complication ($p < 0.001$). In multivariate analysis within the HH group, the Model for End-Stage Liver Disease (MELD) score was an independent predictor of hemothorax (OR = 1.19, 95% CI = 1.03–1.36, $p = 0.012$). **Conclusions:** Repeat thoracentesis is an overall low-risk procedure, although a higher complication rate is observed in HH compared with non-HH patients. The presence of a previous complication significantly increases the risk of future complications in the HH population.

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Introduction

Hepatic hydrothorax (HH) is a transudative pleural effusion that develops in cirrhotic patients with portal hypertension and in the absence of cardiopulmonary dis-

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ease [1]. HH accounts for 2–3% of all pleural effusions [2, 3]. The incidence of HH in cirrhotic patients is reported in varying range (4–15%) in the literature depending on the chest imaging modality [4, 5].

The goal of treatment in HH is to reduce symptomatic pleural fluid caused by ascitic fluid in the pleural cavity. The first step in the management is sodium restriction and diuretic therapy [6]. Approximately 21–26% of these patients suffer from refractory HH and repeat thoracentesis is required for symptom control, particularly when patients are not proper candidates for transjugular intrahepatic portosystemic shunt (TIPS), liver transplant, or are awaiting transplant [7]. Depending on the rate of fluid reaccumulation and symptoms, patients are required to undergo thoracentesis from every few days to every 2–3 weeks. This treatment plan towards alleviating dyspnea is standard practice in the management of HH [6, 8].

Safety profile and complications of thoracentesis as a procedure in general are studied and reported in the literature with a pneumothorax rate of 0.6–6% and hemothorax rate of 0–2% among major complications [9–11]. However, despite routine implementation of repeat thoracentesis as a therapeutic and palliative regimen in HH, the risk profile is not clear. We hypothesize that repeat thoracentesis in patients with HH carries a higher risk secondary to their immunocompromised state with abnormal coagulation factor synthesis and function, bone marrow suppression and thrombocytopenia to name a few. The complication rate of repeat thoracentesis and its safety profile comparing patients with and without HH has not been examined in the literature.

This study was designed to assess the complication rate of repeat thoracentesis in patients with HH and a control group, and explore potential predictive factors for complications in this vulnerable population.

Patients and Method

This is a comparative retrospective case-control study of repeat thoracentesis in patients aged ≥ 18 years with and without HH who underwent thoracentesis at Virginia Commonwealth University (VCU) from January 2010 to September 2015. Charts were reviewed of all cirrhotic patients (identified based on chart-reported coding as well as detailed review of medical history, hepatology consultation review, and implemented treatment strategies) with pleural effusion who underwent thoracenteses.

In parallel, charts of non-cirrhotic patients (non-HH group) were reviewed, with pleural effusion due to etiologies other than HH (malignancy, parapneumonic effusion/empyema, heart or renal failure induced, other) who required thoracentesis within the same time period. It was anticipated that a total of 100 patients with

Table 1. Etiology of pleural effusions and relevant history

Hepatic hydrothorax etiology ($n = 82$)	
Alcoholic cirrhosis	35 (42.7%)
HCV cirrhosis	33 (40.2%)
NASH cirrhosis	14 (17.1%)
History of previous TIPS	19 (23.2%)
Non-hepatic hydrothorax etiology ($n = 100$)	
Malignant pleural effusion	61 (61%)
Parapneumonic/empyema	8 (8%)
Congestive heart failure	16 (16%)
Renal failure	6 (6%)
Other	9 (9%)

HCV, Hepatitis C virus; NASH, non-alcoholic steatohepatitis; TIPS, transjugular intrahepatic portosystemic shunt.

HH would be collected within a 5 years' time period based on which the a priori decision was made to include 100 patients in the control group. The cases were not matched between the two groups. Due to a much larger population of non-HH pleural effusion per year, control group selection was performed from year 2013 (halfway between 2010 and 2015). This timeline was selected to reflect ongoing expertise and complication rates similar to the HH population. Procedural technique, method of supervision and the supervising team were the same within the 5-year time period. Etiology of pleural effusions is provided in Table 1.

For both groups, all thoracenteses recorded in the patients' medical record were included. The VCU Institutional Review Boards approved this study (IRB# HM20002940).

Details of the aspiration procedure are listed in the online supplementary Appendix 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000490001) [12].

Data Collection

Collected data included: number and date of thoracenteses per patient, proceduralists' level of training, admission status, procedure site, volume of fluid removed, and complications. Specific evidence of the following complications was recorded in all cases: pneumothorax, cardiovascular compromise/syncope, hemothorax, infection, re-expansion pulmonary edema, and death. Other collected data included patient demographics, etiology of liver disease, and non-HH pleural effusion. Laboratory data were retrieved from within 72 h prior to and preferably closest to the procedure. Postprocedure pleural fluid analysis labs were retrieved.

Complication Definitions

All prospectively documented complications were recorded, to include all major clinical complications of interest with the following pre hoc definitions:

- Trapped vs. non-trapped lung was recorded separately. When pneumothorax ex vacuo was suspected, chest X-ray was reviewed to verify air in a non-gravity-dependent location with no continued expansion of the air space on follow-up chest X-ray obtained within 6–12 h. Pneumothorax ex vacuo requiring hospitalization or observation was reported under pneumothorax as a complication.

- Re-expansion pulmonary edema (REPE) was diagnosed if there was acute respiratory decompensation with increased work of breathing or oxygen requirement with unilateral pulmonary edema within 24 h.
- Patients were diagnosed with a hemothorax if there was a drop in hemoglobin with rapid re-accumulation of effusion on chest imaging and verified by pleural/serum hematocrit >50%.
- Complications such as continued leak from thoracentesis site were recorded under “other complications.”

Complications were categorized into major (pneumothorax requiring chest tube placement, hemothorax, REPE, and death) and minor (pneumothorax not requiring chest tube placement, pneumothorax ex vacuo, vasovagal syncope, and fluid leak from puncture site) complications.

Statistical Analysis

Simple descriptive statistics were used to describe patient demographics and outcomes. Participants' characteristics were described for the total study sample. Binary and categorical data were reported as percent frequencies. Continuous variables were displayed as mean and standard deviation. Multivariate logistic regression was used to identify the association between severity of liver disease and hemothorax and total complications within the HH group as well as between the two study groups. Severity of liver disease was measured by the Model for End-Stage Liver Disease (MELD) score, which was used as a continuous variable. Platelet count was used as a binary variable with platelet counts above and below $50 \times 10^3/\mu\text{L}$. Akaike information criterion was used to assess goodness of fit and the relative quality of the statistical models.

The Fisher exact test was performed to compare the rate of complications of the first thoracentesis in the HH group with that in control patients. For specific complications, e.g., pneumothorax and hemothorax, the Fisher exact test was performed to compare rates of occurrence between HH and control patients. To analyze the complication rate of repeat thoracentesis, the median number of complications were compared between the patients who had more than 1 thoracentesis, in both the HH and non-HH groups. To account for correlated data from repeated procedures in the same patients, the cumulative rate of complications according to the number of procedures was estimated using the empirical distribution function around the percentage of subjects with complications up to the procedure. For each HH procedure, data were analyzed using associated number of complications, immediate previous complication status, and the accumulated number of complications up to that particular HH procedure, in order to assess the increased complication risk when the subject had a positive complication history.

All statistical analyses were performed with SAS version 9.4. *p* values <0.05 were considered significant.

Results

Baseline Data

462 procedures were recorded and retained in the analysis. A total of 182 patients were included in the study (82 HH and 100 non-HH). Mean age (standard deviation)

Table 2. Procedure characteristics

	274 procedures in the HH group	188 procedures in the non-HH group	<i>p</i> value
Labs			
Mean BUN $\pm$ SD	24.7 $\pm$ 15.6	20.4 $\pm$ 21.4	<0.14
Mean creatinine $\pm$ SD	1.5 $\pm$ 1.2	1.7 $\pm$ 2.0	<0.37
Mean AST $\pm$ SD	83.5 $\pm$ 112.5	57.6 $\pm$ 82.0	<0.001
Mean total bilirubin $\pm$ SD	4.5 $\pm$ 5.6	0.6 $\pm$ 0.5	<0.001
Mean albumin $\pm$ SD	3.0 $\pm$ 1.8	3.4 $\pm$ 0.8	<0.001
Mean WBC $\pm$ SD	7.2 $\pm$ 3.8	11.6 $\pm$ 15.7	<0.001
Mean platelets $\pm$ SD	118.9 $\pm$ 83.5	268.8 $\pm$ 163.7	<0.001
Mean platelets <50 $\times 10^3/\mu\text{L}$	22 $\pm$ 12.4	3 $\pm$ 0.1	<0.001
Mean INR $\pm$ SD	1.7 $\pm$ 0.69	1.3 $\pm$ 0.3	<0.001
Mean MELD score $\pm$ SD	17.7 $\pm$ 6.9	10.1 $\pm$ 7.3	<0.001
Procedure side			
Left	33	67	<0.001
Right	225	121	<0.001
Fluid volume			
Amount of fluid removed $\pm$ SD	2,030 $\pm$ 1,064	1,123 $\pm$ 626	<0.001
Operator training level			
Attending	9	4	<0.30
Trainee (PGY 4–7)	261	184	<0.16
Unknown	4	0	<0.51

SD, standard deviation; INR, international normalized ratio; BUN, blood urea nitrogen; MELD, model for end-stage liver disease; WBC, white blood cell count; AST, aspartate aminotransferase; PGY, postgraduate year; HH, hepatic hydrothorax.

tion) in the HH group was 57 (8.9) and 29 (35.4%) of the patients were female. Mean age (standard deviation) in the non-HH group was 63 (14.3) and 57 (57%) of the patients were female (for procedure characteristics comparing the two groups, see Table 2). Procedure characteristics within the HH group comparing those with and without complications are shown in Table 3.

Procedures and Complication Analysis

There was a median number of 5 (IQR = 3–8) procedures/patient in the HH group and 2 (IQR = 1–4) procedures/patient in the non-HH group. A total of 32.9% (27/82) of HH patients underwent a single thoracentesis during the study period. 55 patients in the HH group (total number of 192 repeat thoracenteses) and 42 patients in the non-HH group (total number of 88 repeat thoracenteses) had more than 1 thoracentesis recorded. Complication details are shown in Table 4.

The rate of any minor and major complication in the non-HH group was 2/188 (1.06%, 95% CI = 0.4–2.5) with

Table 3. Procedure characteristics within the HH group

	257 procedures without compli- cations	17 procedures with complica- tions	<i>p</i> value
Labs			
Mean BUN ± SD	24.6±15.2	26.7±20.6	0.97
Mean creatinine ± SD	1.5±1.2	1.3±0.7	0.74
Mean AST ± SD	84.7±115.6	63.2±31.3	0.56
Mean total bilirubin ± SD	4.2±5.3	7.4±7.9	0.22
Mean albumin ± SD	3.0±1.8	2.8±0.6	0.93
Mean WBC ± SD	7.1±3.8	8.4±3.8	0.12
Mean platelets ± SD	117.3±78.0	141.4±143	0.97
Mean INR ± SD	1.7±0.6	2.2±1.2	0.07
Mean MELD score ± SD	17.6±6.74	19.3±9.0	0.58
Procedure side			
Left	32	1	0.67
Right	209	16	0.31
Fluid volume			
Amount of fluid removed ± SD	2,006±1,082	2,388±686	0.041
Operator training level			
Attending	8	1	0.44
Trainee (PGY 4–7)	245	16	0.57
Unknown	4	0	0.99

SD, standard deviation; INR, international normalized ratio; BUN, blood urea nitrogen; MELD, model for end-stage liver disease; WBC, white blood cell count; AST, aspartate aminotransferase; PGY, postgraduate year; HH, hepatic hydrothorax.

Table 4. Complications

Major complications within the entire cohort (462 procedures)	
Pneumothorax requiring chest tube (95% CI)	0.2% (0.01–1.2)
Hemothorax (95% CI)	1.3% (0.5–2.8)
Re-expansion pulmonary edema (95% CI)	0.8% (0.2–2.2)
Complications within the hepatic hydrothorax group (274 procedures)	
All minor and major complication (95% CI)	6.2% (3.8–9.9)
Pneumothorax (minor and major) (95% CI)	1.5% (0.5–4.0)
Pneumothorax requiring chest tube (95% CI)	0.4% (0.01–2.0)
Hemothorax (95% CI)	1.8% (0.7–4.4)

both complications occurring following a first thoracentesis. Four patients in the HH group had a minor or major complication following their first thoracentesis (4.9%, 95% CI = 1.6–12.7). The rate of any major and minor complication was higher with the first thoracentesis in the HH group compared to the non-HH group but did not reach statistical significance (4.9 vs. 2%, $p = 0.41$). Similarly, the complication rate of second thoracentesis in the HH and non-HH groups were 7.3% (4/55) and 0% (0/42), respectively, but did not reach statistical significance ($p =$

0.12). Additional comparisons were not performed due to a small number of patients with 3, 4, or more thoracenteses in the non-HH group.

No infections in the form of empyema, parapneumonic effusion or cellulitis were recorded, as a result of thoracentesis. All procedures including diagnostic thoracentesis, were also therapeutic. Thoracentesis occurred with the purpose of complete drainage of the pleural space unless limited by trapped lung physiology as per our practice protocol.

Adjusted Analysis

The overall complication rate between the HH and non-HH groups, the overall complication rate in the HH group alone, and hemothorax in the HH group were assessed in the multivariate analysis.

Within the HH group, the odds of developing a hemothorax was 1.2 times higher for every unit increase in the MELD score, after adjusting for international normalized ratio (INR) and platelet count (OR = 1.19, 95% CI = 1.03–1.36, $p = 0.012$) in multivariate analysis. Additionally, the odds of developing a hemothorax was nearly 10 times higher when platelet count was less than $50 \times 10^3/\mu\text{L}$, compared to counts of $>50 \times 10^3/\mu\text{L}$ (OR = 9.67, 95% CI = 1.16–80.42, $p = 0.035$).

In multivariate analysis including variables of age, sex, INR and MELD score within the HH group, the MELD score did not have any significant effect on the total rate of complications (OR = 1.03, $p = 0.39$). For every unit increase in INR, there was a 1.9 times higher overall complication rate (OR = 1.87, 95% CI = 1.08–3.24, $p = 0.024$).

In univariate analysis, the odds of having a complication (minor and major) was 6 times higher in the HH than the non-HH group (OR = 6.15, 95% CI = 1.4–26.9, $p = 0.015$). In multivariate analysis including variables of HH status, BUN and creatinine, the HH group still had higher odds of complication than the non-HH group (OR = 4.91, 95% CI = 1.08–22.2, $p = 0.038$). Additionally, the odds of developing any complication was 4.2 times higher in the HH group after platelet counts were included in the model, but this was not statistically significant (OR = 4.2, 95% CI = 0.9–19, $p = 0.066$).

Repeat Thoracentesis

Repeat thoracentesis was required and performed with shorter intervals in the HH group. Median time interval between repeat thoracentesis was 14 days (IQR = 6–49) in the HH group and 35 days (IQR = 11–115) in the non-HH group. The median number of all complications of repeat thoracentesis was compared between the HH and

Table 5. Cumulative rate of complications against the number of thoracentesis

Proce- dure number	Number of subjects	Number of subjects with complications at the <i>n</i> th procedure	Number of subjects with complications up to the <i>n</i> th procedure	Cumulative rate of complications (%)
1	82	4	4	4.87
2	55	4	6	7.32
3	36	1	6	7.32
4	28	3	8	9.76
5	19	2	9	10.98
6	15	2	10	12.2
7	13	1	10	12.2
8	7	0	10	12.2
9	6	0	10	12.2
10	5	0	10	12.2
11	2	0	10	12.2
12	2	0	10	12.2
13	1	0	10	12.2
14	1	0	10	12.2
15	1	0	10	12.2
16	1	0	10	12.2

Fig. 1. The cumulative rate of complications against the number of thoracentesis. The cumulative rate of complications increases with the number of thoracenteses. The overall complication rate at thoracentesis number 2 (55 patients) in the HH population is at 7.3% and reaches nearly 10% at thoracentesis number 4. Within the control population, no complications are seen at thoracentesis number 2 (42 patients) or the following thoracenteses.

non-HH group, demonstrating an 8.1% risk (from 2nd thoracenteses) in the HH group compared with a 0% risk in the non-HH group ($p = 0.016$, 95% CI = 1.5–14.6%).

Ten patients (12.2%) in the HH group had at least 1 minor or major complication at any point. A detailed review of the data showed that out of the 10 patients with 20 complications in 17 procedures, 6 patients had 1 complication only, and the remaining 4 patients had a total of 14 complications.

The cumulative rate of complications increased with the increased number of thoracenteses. The complication rate for repeat thoracentesis in the non-HH group was zero, regardless of the number of thoracenteses (Table 5; Fig. 1).

In multivariate analysis adjusted for INR, platelet count, and the MELD score, having an immediate previous complication significantly increased the risk of having another complication (OR = 17.1, $p = 0.0013$). Having more than 1 previous complication (not necessarily an immediate previous complication) significantly increased the risk of future complications (OR = 15.0, $p < 0.001$).

Details of each complication can be found in online supplementary Table S6.

Discussion

Although repeat thoracentesis is considered as a treatment for refractory symptomatic effusion in HH, the risk of repeat thoracentesis is not well reported in the literature. To our knowledge, this is the first study to examine the safety of repeat thoracentesis in HH patients compared to a non-HH control group [9, 10, 13, 14].

We have demonstrated that the major complication rate in our cohort of 462 patients is comparable to the world published literature for thoracentesis [9–11, 15, 16]. Total and major complication rates were found to be higher in the HH than the non-HH group.

Castellote et al. [17] retrospectively reviewed the complications of thoracentesis in cirrhotics with HH assessing the complication rate in 69 patients (245 thoracenteses). The pneumothorax rate in the diagnostic group was 4.4%, but rose to 7.7% in the first therapeutic thoracentesis. By thoracentesis number 4, the pneumothorax rate was 34% (95% CI = 22.1–47.2). The authors concluded that therapeutic thoracentesis ($\geq$ thoracentesis number 2) is a risk factor for pneumothorax and the risk increases with consecutive thoracenteses. Our data does not show a significant change in pneumothorax rate associated with repeat thoracentesis. Although in our cohort,

the overall complication rate was higher in the HH vs. non-HH group, the total pneumothorax rate was very low. While it is difficult to consider the possible causes of a high pneumothorax rate in the study by Castellote et al. [17], we speculate that these findings may be explained by the lack of ultrasound use for puncture site identification, among other possible reasons such as trapped lung physiology and pneumothorax ex vacuo.

Our data show that having a previous thoracentesis complication of any kind increased the chance of having a complication with another thoracentesis by 15-fold. This risk was even higher if the previous complication involved the immediate last thoracentesis. While it is impossible to prove the causality of these findings with a retrospective design, we hypothesize that in a patient with end-stage liver disease, the presence of a complication may indicate abnormal pleural space anatomy or physiology (e.g., intercostal varicose veins are reported in patients with end-stage liver disease [18]). A higher complication rate following a prior complication may indicate worsening downstream effects of liver failure, hypoalbuminemia resulting in hypotension and rapid flux of fluid through the diaphragm, worsening coagulopathy, and scar tissue formation at the site of prior puncture site, resulting in future procedural complexities. In multivariate analysis, the overall complication rate remained significantly higher in the HH group. The MELD score and platelet count were independent predictors of hemothorax. The role of transfusion was not evaluated in this study. Whether thrombocytopenia is a marker of bone marrow dysfunction and poor health state or the primary cause of hemothorax is not known.

In this study, univariate analysis showed that among the HH group, total complications (but not REPE alone) were more likely to occur following a larger volume thoracentesis ($p = 0.0412$; Table 3). A study by Feller-Kopman et al. [19] noted that large-volume thoracentesis was not associated with REPE. Additional trials are required to further investigate this question.

The results of this study highlight the risks and safety of thoracentesis in pleural effusion management in HH. This is particularly important when patients are poor candidates for TIPS and/or are awaiting liver transplant evaluation [20–25]. Chest tube drains are shown to carry a high complication rate with electrolyte imbalance, renal failure, infection, and death [26–28]. In a prospective study of 24 patients with HH, Chen et al. [29] have shown that the use of indwelling pleural catheters (IPCs) with a regimented drainage schedule of 1 L fluid removal on every other day may be a feasible and safe approach. Although IPCs are often used in the management and pal-

liation of malignant pleural effusion [30–32], a growing body of literature proves their utility and safety in benign pleural effusions [29, 33–35]. However, this is paired with an overall higher complication rate and lower spontaneous pleurodesis rate in the HH population receiving IPCs compared to malignant pleural effusion [29, 36]. This study shows that repeat thoracentesis is an overall low-risk procedure in both the HH and non-HH population. However, when repeat thoracentesis is clinically required in the HH population, we suggest that particular attention be paid to the history of prior complications, severity of liver disease, and presence of thrombocytopenia.

There are a number of limitations in our study. Firstly, this is a single-center retrospective design lending itself to the possibility of missing or inaccurate data. We have a dedicated policy in place to stop anticoagulation, where patients are allowed to continue on Aspirin, whereas other anticoagulants are ceased according to half-life and pharmacokinetics. In this study, we did not specifically review every case to assess the length of time that anticoagulation was discontinued in those receiving such medications, accepting that the policy as above was operational. Additionally, due to few overall complications in the cohort, model building was limited to a small number of variables per model. The results of this study will need to be evaluated and confirmed in a larger prospective design.

This study does not assess the efficacy of repeat thoracentesis in symptom management. Large-scale and prospective randomized trials are needed to fully evaluate safety and assess quality of life, using repeat thoracentesis compared with other modes of management.

Conclusion

Repeat thoracentesis is an overall low-risk procedure in the HH and non-HH population but the safety profile is lower in the HH group. Cirrhotic patients with refractory HH with a history of a previous thoracentesis complication have a significantly higher risk of developing future thoracentesis complications. Hemothorax risk is increased with a higher MELD score and thrombocytopenia in HH. We recommend meticulous study of the patients' physical and clinical state to reconsider the indications of thoracentesis in patients with a thoracentesis complication history. Candidacy for alternative methods such as TIPS and transplantation should be re-examined when possible. Other modes of management such as IPC placement in this patient population are under investigation and should be compared with repeat thoracentesis in re-

fractory HH management. Additional studies are required to evaluate the efficacy of repeat thoracentesis in symptom management and palliation in HH.

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Disclosure Statement

Dr. Shojaei has no conflicts of interest to declare. Dr. Khalid has no conflicts of interest to declare. Dr. Kallingal has no conflicts of interest to declare. Dr. Kang has no conflicts of interest to de-

clare. Dr. Rahman has received an unrestricted educational grant from Rocket Medical and provides clinical advice to them and reports no other potential conflicts related to the manuscript.

Author Contributions

Dr. Shojaei participated in the study design, data collection, data analyses, manuscript writing, and manuscript review. Dr. Khalid participated in data collection and manuscript review. Dr. Kallingal participated in data collection and manuscript review. Dr. Kang participated in data analyses and manuscript review. Dr. Rahman participated in study design, data analyses, manuscript writing, and manuscript review.

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