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Incidence and risk factors for postoperative delirium after liver transplantation: a systematic review and meta-analysis

S. ZHOU[2], F. DENG[1], J. ZHANG[1,3], G. CHEN[1]

[1]Department of Anesthesiology, The Third Xiangya Hospital of Central South University, Changsha, Hunan, China
[2]Academic Affairs Department, Changsha Medical University, Changsha, Hunan, China
[3]Department of Breast Surgery, Tangshan Central Hospital, Tangshan, Hebei, China

Abstract. – OBJECTIVE: Postoperative delirium (POD) is a common complication after surgery. The incidence of POD and delirium risk factors after liver transplantation (LT) have not been systematically summarized.

MATERIALS AND METHODS: Databases, such as PubMed, Cochrane Library, and EMBASE were searched up to September 15, 2019. All relevant studies that addressed the incidence and risk factors for POD after LT were included and summarized.

RESULTS: Twenty articles with 3417 patients with LT were included. The pooled overall incidence for POD after LT was 0.16 (95% CI 0.12-0.22). The overall incidence (0.24, 95% CI 0.15-0.35) in Asians was higher than in Caucasians (0.13, 95% CI 0.08-0.19). Encephalopathy (OR 4.16, 95% CI 2.59-6.68, $p<0.01$), alcoholic liver disease (OR 2.25, 95% CI1.46-3.47, $p<0.01$), MELD score, midazolam use, duration of ICU stay (day), and duration of hospital stay (day) were significantly associated with POD. POD was a mortality risk factor according to the pooled results of ICU mortality (OR 5.06, 95% CI 1.42-17.99), in-hospital mortality (OR 4.05, 95% CI 1.86-8.84), and one-year mortality (OR 4.21, 95% CI 1.94-9.12).

CONCLUSIONS: POD is common after LT and leads to a worse outcome. Several risk factors were consistently associated with POD after LT. The risk factors identified by this study may benefit the prevention and diagnosis of POD. This study is the first to summarize the occurrence of POD after LT.

Key Words:
Postoperative delirium, Liver transplantation, Incidence, Risk factor, Meta-analysis.

Introduction

Delirium is an acute state featured by mental confusion and emotional disruption[1]. It is associated with the onset of dementia and substantial morbidity[2,3]. Moreover, delirium is a relatively common complication in critically ill patients with increased stay length in an intensive care unit (ICU) and higher mortality[4]. Besides, postoperative delirium (POD) incidence is as high as 3.3% to 77%[5].

The delirium rate after liver transplantation (LT) has been reported to be 10%[6] and 47%[7] for deceased-donor organ recipients and living-donor organ recipients, respectively. It can be caused by metabolic disturbances, infections, organ failure, hepatic or uremic encephalopathy, or neurotoxic side effects from immunosuppression medications, such as calcineurin inhibitors or high-dose steroids[8]. Several previous studies assessed the risk factors and courses of delirium specific to LT. However, the results are conflicting[9-11].

Up to now, the incidence and risk factors of delirium after LT has not been systemically summarized. Given that delirium is associated with poor outcomes mentioned above, this topic's systematic assessment might improve the prevention, diagnosis, and treatment of POD after LT.

Materials and Methods

Literature Search

We used the individual and combined keywords of "Liver Transplantations", "Delirium", and "Risk Factors" to search for relevant articles according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Supplementary Material**)[12]. Several databases, such as PubMed, Cochrane Library, and EMBASE, were used to identify articles published up to September 15, 2019. The

Corresponding Author: Gong Chen, MD; e-mail: chengong86@csu.edu.cn

bibliographies and articles that cited relevant studies were checked to include additional relevant studies.

Eligibility Criteria

The eligibility criteria for the potential studies were (1) observational studies, (2) participants underwent LT, (3) validated tools for assessment delirium were used, (4) at least one risk factor for delirium was identified, (5) all needful information could be extracted, and (6) publication language was English.

Short reports, communications, abstracts or posters for conferences, review articles, and non-human studies were excluded. For the study population reported in duplication, only the inclusive one was included.

Data Extraction

The articles were identified independently by two authors (Gong Chen and Juan Zhang). For each included study, a uniform table was used to obtain the necessary data. All disagreements were solved by a discussion of the two reviewers to reach a consensus. For all included studies, the characteristics of the articles (e.g., the authors, year of publication, and country), participant characteristics (e.g., mean age and sex ratio), delirium diagnosis tool, the incidence of delirium, and the odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for all identified risk factors were extracted.

Quality Scoring of Studies

The Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the included studies[13]. The NOS was assessed according to three factors: (1) selection process of the cases (three items), (2) comparability of the two study groups (two items), and (3) evaluation process of the outcome (two items).

One point was awarded if the item was "yes" for the participants' selection and outcome assessment. One or 2 points were be given for each item of comparability. The NOS for each study was between 2 and 9 points. To distinguish the studies' study quality, 0 to 4 points indicated low quality, 5 to 6 indicated moderate quality, and 7-9 indicated high quality.

Statistical Analysis

The inverse variance methods with random effect were used to pool the OR estimates with their corresponding 95% CIs or mean difference (MD) for continuous data of the included studies. An analysis was conducted if at least two articles assessed similar risk factors with comparable methods.

The heterogeneity among included studies was assessed with the I^2 statistic, which evaluates the percentage of variability. The cutoff values of I^2 for low, moderate, and high heterogeneity were <25%, 25%-50%, and >75%, respectively[14]. The Begg's rank correlation[15] and Egger's weighted regression methods[16] were used to assess the publication biases. Subgroup analyses were conducted according to the study participant features or outcomes. Forest plots and statistical analyses were generated with Review Manage (version 5.3, The Cochrane Collaboration, Oxford, UK). STATA 15.0 (Stata Corporation, College Station, TX, USA) was used to assess the Begg's and Egger's tests. All p-values <0.05 were deemed statistically significant.

Results

Study Selection

Ultimately, 441 articles were identified by the initial search, and 202 were excluded due to overlaps. After browsing the titles or abstracts, 185 were excluded. Ultimately, 20 studies[7,9-11,17-32] were included for data analysis after retrieving 54 full-text papers. The flowchart for potential study inclusion is shown in Figure 1.

Study Characteristics

Twenty articles with a total of 3417 patients who underwent LT were included in the study. All studies provided data on incident delirium, and 664 were diagnosed as POD. The features of the study participants are summarized in Table I. The included studies' sample size ranged from 40 to 512, and these studies were published from 1986 to 2018. Six studies were conducted in United States[19,26-30], three in the Republic of Korea[9,22,31], three in Taiwan[11,20,24], two in Argentina[18,21], one in Turkey[23], one in Spain[25], one in Japan[32], one in France[7], one in Switzerland[10], and one in Germany[17]. Five were prospective studies[10,26-29], and fifteen were retrospective studies[7,9,11,17-25,30-32]. One study did not report the percentage of males[24], but the percentage ranged from 38.46% to 74.40 % for the 19 other studies.

Quality Assessment

NOS for the included studies can be found in **Supplementary Table I**. All included studies

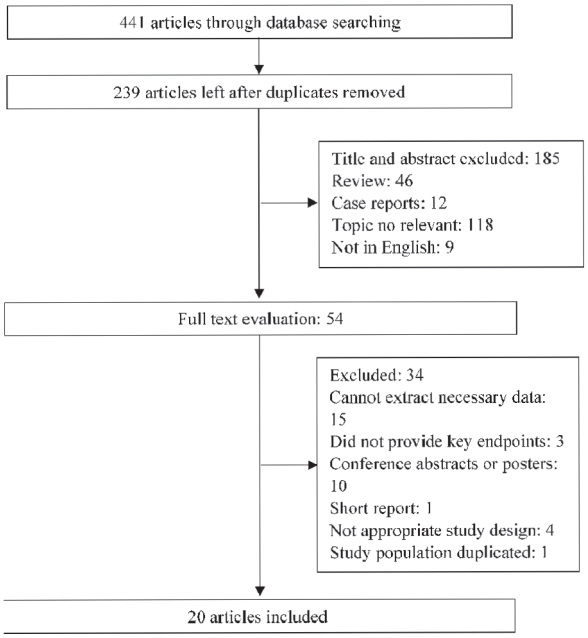

Figure 1. Flow chart of the study selection.

were assessed as higher quality. Four studies were assessed as 6 points, 11 as 7 points, and 5 as 8 points.

Incidence of POD

All 20 included studies provided the incidence of POD, and the range of the incidences was from 0.01 to 0.47. When summarizing the incidences, the pooled incidence was 0.16 (95% CI 0.12-0.22) with a moderate heterogeneity (I^2= 78%). More data can be found in Figure 1.

In order to determine the sources of heterogeneity, sensitivity analyses were performed by dividing the studies into two groups by the ethnicity of the study population. The Asian group included 7 studies [9,11,20,22,24,31,32] from Taiwan, Japan, and the Republic of Korea, and the Caucasian group included 13 studies[7,10,17-19,21,23,25-30] conducted in Western countries. The overall incidence (0.24, 95% CI 0.15-0.35) among Asians was higher than among Caucasians (0.13, 95% CI 0.08-0.19). The I^2 values were slightly decreased to 58% and 69% for the two groups, respectively. When we excluded the studies conducted in the United States from the Caucasian group, the overall incidence was 0.21 (95% CI 0.18-0.25) with an acceptable heterogeneity (I^2=25%). Additional data are presented in Figure 2 and Figure 3.

Risk Factors of POD

From the included studies, 192 risk factors were included for the individual analyses, and 56 of them were significant. Ultimately, 21 risk factors were pooled, and the corresponding ORs or the MDs were extracted. The risk factors are shown in Table II. Six risk factors [age, Model for End-stage Liver Disease scores (MELD score)], duration of surgery, midazolam use, duration of ICU stay, and hospital stay) were pooled by MDs.

Five studies[10,11,19,27,28] with 156 POD patients and 463 patients showed age to be a risk factor for POD. The pooled MD of age was 2.21 years (95% CI-0.56 to 4.99, p=0.12, I^2=0%). Male sex and being married were reported in six and two studies, respectively. The pooled result indicated both male sex and being married were not associated with POD.

Regarding medical history, diabetes mellitus and encephalopathy were assessed. According to pooled results, encephalopathy was a risk factor for POD by two studies (OR 4.16, 95% CI 2.59-6.68, p<0.01, I^2= 0%).

Alcoholic liver disease, hepatocellular carcinoma, viral hepatitis, and primary biliary cirrhosis were summarized to assess the association between liver disease etiology and POD. Alcoholic liver disease was found to be associated with POD (OR 2.25, 95% CI 1.46-3.47, p<0.01, I^2=0%).

Liver/kidney surgery, MELD score, and surgery duration (min) were pooled to assess the associations between transplant details and POD. MELD score with MD of 4.63 (95% CI 1.72-7.54) was a risk factor of POD.

Regarding postoperative factors, midazolam use, duration of ICU stays (day), and duration of hospital stay (day) were found to be risk factors with MDs of 5.00 (95% CI 3.83-6.18), 5.05 (95% CI 1.96-8.13), and 18.32 (95% CI 1.98-34.65), respectively.

POD was supposed to be a mortality risk factor according to the pooled results of ICU mortality (OR 5.06, 95% CI 1.42-17.99), in-hospital mortality (OR 4.05, 95% CI 1.86-8.84), and one-year mortality (OR 4.21, 95% CI 1.94-9.12).

All the pooled risk factors and outcomes are presented in Table II and **Supplementary Table II**, respectively. The forest plots for each risk factor and outcome can be found in the **Supplementary Figures**. No heterogeneity was observed for the risk factors, and the heterogeneity for each pooled process can be found in the **Supplementary Figures**.

Table I. Characteristics of the included studies.

Studies	Country/region	Study design	Age, years (means ± SD)	Percentage of male	Criteria for POD	Screening frequency	Incidence of POD (n/N)t
Trzepacz et al, 1986[29]	United States	Prospective	40.00 (18.00-58.00)[a]	60.00%	DSM-III	72 h	12/40
Trzepacz et al, 1988[28]	United States	Prospective	40.20 ± 12.90	64.81%	DSM-III	72 h	18/108
Trzepacz et al, 1989[27]	United States	Prospective	41.30 ± 11.10	62.75%	DSM-III	72 h	46/247
Burkhalter et al, 1994[26]	United States	Prospective	17.00-68.00 a	54.00%	DSM-III	Symptom driven	16/100
Margarit et al, 1998[25]	Spain	Retrospective	50.00 (19.00-64.00)[a]	71.42%	DSM-III	Symptom driven	1/84
Noma et al, 2008[32]	Japan	Retrospective	47.30 ± 11.40	38.46%	DSM-IV	Symptom driven	9/91
Chiu et al, 2009[24]	Taiwan	Retrospective	52.60 ± 7.50	NA	DSM-IV	Symptom driven	8/168
Yilmaz et al, 2011[23]	Turkey	Retrospective	38.00 (1.00-68.00)[a]	62.20%	DSM-IV	24 h	3/172
Lee et al, 2013[22]	Republic of Korea	Retrospective	51.00 ± 9.570	74.40%	DSM-IV	48 h	200/512
Lescot et al, 2013[7]	France	Retrospective	60.00 (49.00-65.00)[a,b]/ 58.00 (51.00-63.00)[a,b]	64.30%	DSM-IV	48 h	28/309
Wang et al, 2014[11]	Taiwan	Retrospective	53.40 ± 8.40	74.40%	RASS	12 h	37/78
Pinero et al, 2014[21]	Argentina	Retrospective	53.00 ± 12.00	46.30%	APA	72 h	5/41
Lee et al, 2014[31]	Republic of Korea	Retrospective	NA	69.23%	DSM-IV	8 h	56/130
Wu et al, 2016[20]	Taiwan	Retrospective	52.30 ± 9.81	73.96%	DSM-IV	36 h	75/288
Oliver et al, 2017[30]	United States	Retrospective	58.33/57.20	64.64%	DSM-IV	48 h	38/181
Bhattacharya et al, 2017[19]	United States	Retrospective	51.80	66.70%	DSM-IV	48 h	36/144
Beckmann et al, 2017[10]	Switzerland	Prospective	55.00 ± 10.90	69.00%	ICDSC	24 h	19/42
Piñero et al, 2018[18]	Argentina	Retrospective	53.00 (42.00-60.00)[a]	40.10%	APA	48 h	5/307
Kork et al, 2018[17]	Germany	Retrospective	55.20 ± 16.20	46.70%	DSM-IV	24 h	9/122
Lee et al, 2018[9]	Republic of Korea	Retrospective	54.00 (18.00-76.00)[a]	70.35%	CAM	24 h	43/253

Abbreviations: SD, standard deviation; POD, postoperative delirium; DSM, Diagnostic and Statistical Manual of Mental Disorders; CAM, Confusion Assessment Method; ASS, Richmond Agitation-Sedation Scale; APA, American Psychiatric and Critical Care Associations guidelines; ICDSC, German version of the 8-item Intensive Care Delirium Screening Checklist; NA, not available. [a]Range of age. [b]Means for delirium and without delirium group.

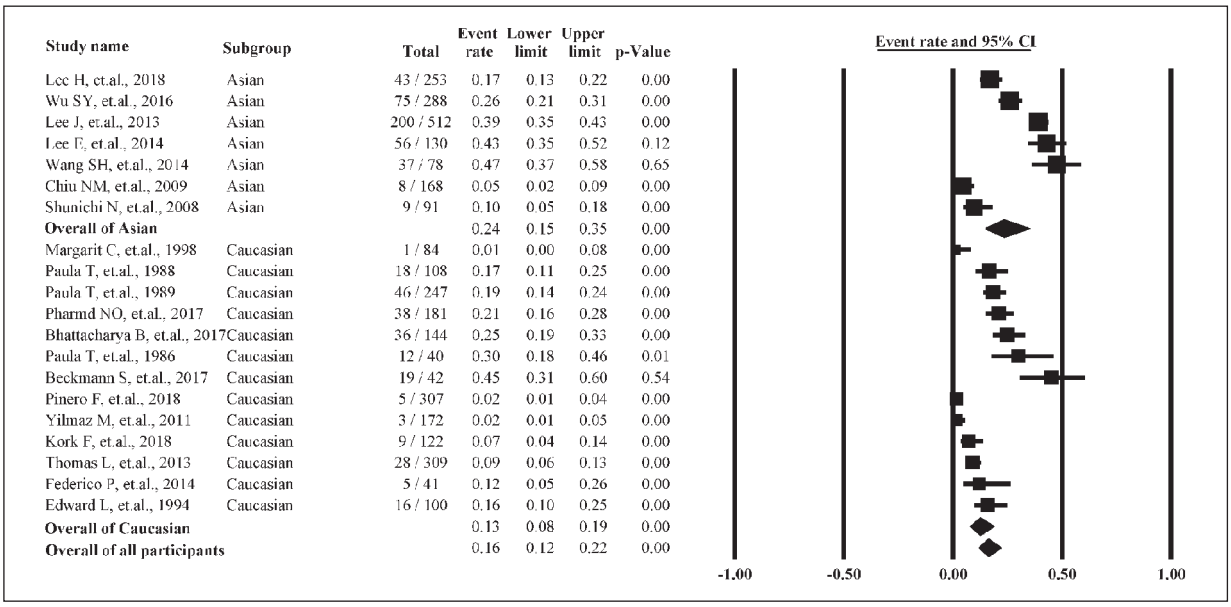

Figure 2. Summarized incidence of postoperative delirium.

Publication Bias

All the potential publication biases were less than 0.05 for Begg's rank correlation analysis and Egger's weighted regression analysis. The *p*-values are presented in the **Supplementary Table III**.

Discussion

As far as we know, the current meta-analysis is the first study that systematically summarized the incidence and the risk factors of POD after LT. Twenty studies[7,9-11,17-32] with 3417 patients after LT were included and summarized. The overall incidence of POD was 0.16, and the overall incidence (0.24, 95% CI 0.15-0.35) in Asians was significantly higher than in Caucasians (0.13, 95% CI 0.08-0.19). Encephalopathy, alcoholic liver disease, MELD score, midazolam use, duration of ICU stays (day), and hospital stay duration were significantly associated with POD. POD had a significant burden of mortality.

Neurological complications, both preventable and treatable, such as delirium, are identified among about 30% of the patients and occurred mostly during the first month after LT[33]. In this study, the higher incidence of POD in LT was consistent with vascular surgical patients 23.4% (range, 4.8%-39%)[34] and major head and neck cancer surgery patients (ranged from 11.50% to 36.11%)[35]. The incidence in Asians was significantly higher than in Caucasians, possibly because of ethnic differences.

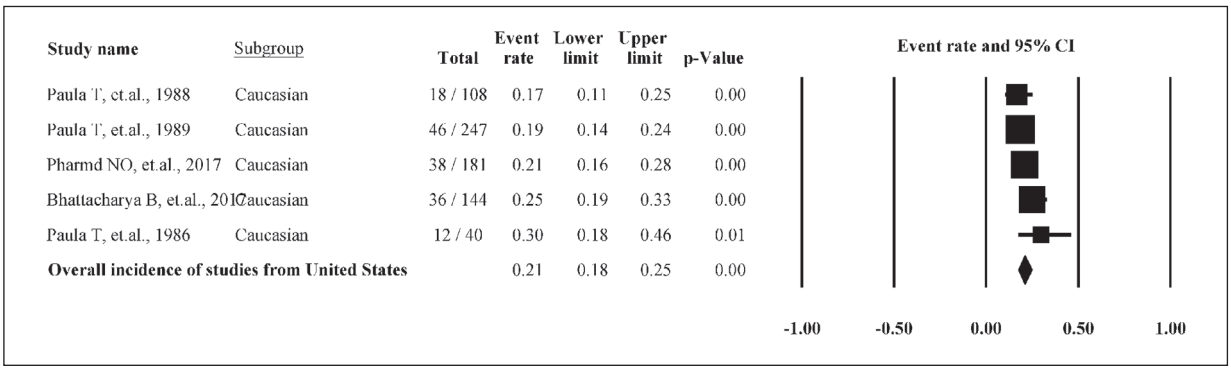

Figure 3. Summarized incidence of postoperative delirium of the studies from the United States.

Table II. Meta-analysis of risk factors for postoperative delirium (reported more than once).

Risk factors	Number of studies	Number of PODs	Number of without POD	Pooled OR or MD [95%CI]	p-values	I^2 Heterogeneity (%)
Age 5	156	463	2.21 (-0.56-4.99)[a]	0.12	35%	
Male sex 6	201	806	0.90 (0.64-1.27)	0.55	0%	
Married 2	56	64	0.60 (0.23-1.59)	0.31	0%	
Medical history						
Diabetes mellitus	2	80	251	1.35 (0.70-2.62)	0.37	0%
Encephalopathy	4	146	675	4.16 (2.59-6.68)	< 0.01	0%
Etiology of liver disease						
Alcoholic liver disease	5	163	108	2.25 (1.46-3.47)	< 0.01	1%
Hepatocellular carcinoma	2	24	132	0.52 (0.29-0.95)	0.03	0%
Viral hepatitis	4	127	322	0.77 (0.30-1.98)	0.59	75%
Primary biliary cirrhosis	2	65	322	1.15 (0.24-5.59)	0.86	0%
Coexisting conditions						
Hypertension	2	79	318	1.02 (0.55-1.89)	0.95	0%
Transplant details						
Liver/kidney	3	117	461	1.70 (0.91-3.17)	0.09	0%
MELD score	2	73	149	4.63 (1.72-7.54)[a]	< 0.01	0%
Duration of surgery (min)	2	73	149	4.97 (-53.25-63.18)[a]	0.87	55%
Postoperative factor						
Midazolam use (mg)	2	79	318	5.00 (3.83-6.18)[a]	< 0.01	0%
Duration of ICU stay (day)	2	73	149	5.05 (1.96-8.13)[a]	< 0.01	0%
Duration of hospital stay (day)	2	73	149	18.32 (1.98-34.65)[a]	0.03	0%

Abbreviations: POD, postoperative delirium; OR, odds ratio; MD, mean difference; CI, confidence interval; ICU, Intensive Care Unit; MELD scores, Model for End-stage Liver Disease scores. [a]Indicates that the mean difference is reported.

All included studies in this meta-analysis examined a range of LT patients and covered many risk factors between patients with or without POD. In the present study, encephalopathy, alcoholic liver disease, MELD score, midazolam use, duration of ICU stays (day), and hospital stay duration were significantly associated with POD. The comorbidities and encephalopathy were significantly associated with POD. Dhar et al[8] showed that encephalopathy was associated with POD and occurred during the first month after LT. By assuming that predominantly pre-LT comorbidities and early intra- and postoperative factors likely affected the pathogenesis of POD, the risk factors could be used to screen the high-risk patients for POD after LT. Moreover, that may allow clinicians to deploy multi-component POD prevention strategies appropriately.

One consistency with the literature regarding POD after LT is the effect on outcomes. LT patients who developed POD had longer hospital and ICU stays and higher 1-year mortality, consistent with previous studies indicating worse outcomes in vascular surgical patients[34] and older patients undergoing gastrointestinal surgery[36]. Delirium is more frequently diagnosed in sicker patients. Therefore, establishing whether delirium is the cause of a patient's critical condition is impossible. Given the costs of extended ICU and hospital lengths of stay in addition to more diagnostic studies and procedures, developing delirium poses an economic burden. Identifying risk factors for developing delirium is useful if we can improve delirium incidence in high-risk patients. Still, the identification of POD may cause poor outcomes, and an economic burden may draw physicians or researchers' attention on this issue. In the future, more studies are needed to identify more cases undergoing risk factors of delirium as protocol-based management may achieve better outcomes cost-effectively.

When interpreting the result of the current research, we still need to address the limitations. First, POD was defined by a variety of methods. The differences in delirium evaluation among the studies might cause methodological limitations and compromise the result. Second, most of the risk factors could not be pooled because they were identified only once among the included studies, and they need to be confirmed in a future study. Third, most included investigations[10-11,17-19,21,23-27,28-32] had a limited sample size. Due to the smaller sample size of some studies, we could not perform additional stratification

analyses. Fourth, many studies[7,9-11,19-20, 22-25, 26-32] did not match the cases by age or sex. As a result, the mean age and the sex ratios among RCTs were varying, which might cause heterogeneity. Fifth, bias might exist due to only English articles were included.

Conclusions

Even though many researches examined the occurrence of POD after surgery, this meta-analysis is the first to summarize the occurrence of POD after LT, based on 20 articles from 10 countries, and pooled a large dataset of 664 patients with POD and 3753 without POD after LT. The results show that POD incidence after LT was as high as 0.16, and Asia countries had a higher incidence than Caucasians. Several risk factors were identified in this study, and that may enhance future studies to explore the extent of their effects. POD was found to be a significant risk factor for mortality. In the future, by stratifying patients, intervention studies could be planned by the risk factors identified, which might benefit the improvements in patient care. The risk factors that were not validated in the current study need to be confirmed in future studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Authors' Contribution

GC and JZ carried out the studies, participated in collecting data, and drafted the manuscript. SZ and FD performed the statistical analysis and participated in its design. SZ and FD helped to draft the manuscript. All authors read and approved the final manuscript.

Supplementary Materials

See **Supplementary Tables I-III** and **Supplementary Figures 1-21** in the **Supplementary Material** for comprehensive image analysis.

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