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Preexisting Diabetes Elevates Risk of Local and Systemic Complications in Acute Pancreatitis

Systematic Review and Meta-analysis

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Abstract: The prevalence of diabetes mellitus (DM) and acute pancreatitis (AP) increases continuously, therefore, to understand the effects of preexisting diabetes on AP is crucially needed. Here, we performed a systematic review and meta-analysis in which AP patients including DM and non-DM groups were sorted. Several outcome parameters were analyzed, and the odds ratio (OR) and standardized mean difference with 95% confidence intervals (CIs) were calculated.

We found 1417 articles, of which 9 articles involving 354,880 patients were analyzed. More complications were seen in diabetic patients than in non-DM patients (OR, 1.553 [95% CI, 1.266–1.904]; $P < 0.001$). Intensive care unit admission (OR, 1.799 [95% CI, 1.442–2.243]; $P < 0.001$) and renal failure (OR, 1.585 [95% CI, 1.278–1.966]; $P < 0.001$) were more frequent in DM patients. There was a tendency of higher mortality and local complications (OR, 1.276 [95% CI, 0.991–1.643]; $P = 0.059$; and OR, 1.267 [95% CI, 0.964–1.659]; $P = 0.090$, respectively) in preexisting DM. Length of hospitalization was longer in DM patients (standardized mean difference, 0.217 [95% CI, 0.075–0.360]; $P = 0.003$). Preexisting DM negatively influences the outcome of AP and increases the risk of renal failure, local complications, and mortality.

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Acute pancreatitis (AP) is a severe inflammatory condition with increasing incidence and hospitalization worldwide.[1,2] Acute pancreatitis has a variable severity ranging from mild and self-limited to severe and fatal. The mortality of the disease ranges approximately from 2 to 5% and depends on the development of organ failure and local complications, which are summarized in the revised 2012 Atlanta classification.[3] The major etiological factors are gallstones and alcohol intake,[1] but hypertriglyceridemia and intake of certain medications may also be present in the background.

The global prevalence of diabetes among adults doubled between 1980 and 2014.[4] The relationship between AP and diabetes mellitus (DM) is complex. Acute pancreatitis may result in DM.[5] On the other hand, patients with type 2 (T2) DM had an elevated risk of AP,[6–10] and the risk of AP in diabetic patients can be reduced with appropriate glycemic control.[11] Furthermore, DM patients tend to develop hypertriglyceridemia and gallstones, both of which may lead to AP.[12,13] Hyperglycemia was demonstrated to be closely correlated with poor outcomes of morbidity and mortality in critically ill patients.[14] Many patients with T2DM have comorbid conditions (eg, heart failure, renal disease, liver disease, and obesity), which may increase the risk of severe AP and can be strong predictors of early death from AP.[15,16] Moreover, diabetic comorbidities require the use of medications that have been associated with pancreatitis. Incretin use in the treatment of T2DM has been investigated in several meta-analyses of the risk of AP.[17–21]

Experimental studies clearly suggest that preexisting diabetes deteriorates the outcome of AP. Zechner et al[22] showed that diabetes significantly raises the plasma interleukin 6 concentration and further reduces the number of lymphocytes during AP; diabetes thus exacerbates pancreatitis-induced systemic inflammation. Other studies have also demonstrated that diabetes increases pancreatic fibrosis[23,24] and decreases pancreatic regeneration.[25–27] Importantly, cholecystokinin-promoted pancreatic regeneration was also impaired in diabetic rats after the induction of experimental pancreatitis.[28]

Unfortunately, little human data are available on the effect of preexisting DM or the complications of AP. No systematic reviews or meta-analyses are available to summarize our knowledge of the effects of preexisting diabetes on the outcome of AP.

In this study, we therefore aimed to demonstrate the influence of preexisting DM on the outcomes of AP, including mortality, length of hospitalization (LOH), incidence of organ failure, and intensive care unit (ICU) admission in a large number of patients by using detailed meta-analyses of the data available in the literature.

MATERIALS AND METHODS

Search Strategy

This study was conducted according to the principles in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement[29] (Supplementary Table 1, http://links.lww.com/MPA/A663) and was registered in the PROSPERO registry (under registration number CRD42016053207). Our meta-analysis was based on the patient, intervention, comparison, and outcome (PICO) format (P, patients suffering from AP; I, diabetic patients; C, nondiabetic patients; O, mortality, LOH, organ failure, ICU admission). A systematic search was made in 3 databases, Pubmed, Embase, and the Cochrane Library, using the following terms: *acute pancreatitis* and *diabetes mellitus*. The search was limited to human data and to full-text English articles. The exact search terms in Pubmed were as follows: (*acute*[all fields] and (*pancreatitis*[MeSH terms] or *pancreatitis*[all fields])) and (*diabetes mellitus*[MeSH terms] or (*diabetes*[all fields] and *mellitus* [all fields]) or *diabetes mellitus*[all fields]) and (*humans*[MeSH terms] and English[lang]). The database search was conducted up to March 8, 2017. The duplicates were removed using the EndNote X7 reference manager software (Clarivate Analytics, Philadelphia, Penn).

Study Selection

The studies were selected separately by two investigators (A.M. and L.C.). Disagreements were resolved by consulting a third reviewer (P.H.). Clinical studies were eligible provided that they reported the data for adult patients suffering from AP separately for diabetic and nondiabetic patients. Information on the outcome of pancreatitis (mortality, organ failure, LOH, and admission to ICU) was searched for manually (Supplementary Table 2, http://links.lww.com/MPA/A663). The reference lists in the articles obtained were also checked, but no additional eligible articles were found.

Data Extraction

For statistical analysis, mortality data were calculated by number of patients[30,31]; local complications[32] and renal failure data[33] were expressed as percentages. The data for Supplementary Table 2 (http://links.lww.com/MPA/A663) from Mole et al[34] were computed, and the percentage for ICU admission was calculated for the DM and non-DM groups. Kikuta et al[30] presented graphs on organ failures in DM and non-DM groups each day in the first 72 hours. These data were confirmed by the investigators, and an average value was calculated from data for 3 days. Nawaz et al[35] only presented the median for LOH. The interquartile range for these data was requested for statistical analysis.

The basic characteristics of the 9 eligible articles included in the meta-analysis are shown in Table 1.

Data Synthesis and Analysis

All meta-analysis calculations were made with Comprehensive Meta-Analysis software version 3 (Biostat, Inc., Englewood, NJ) using the random effects model (DerSimonian-Laird method[39]). Odds ratios (OR) and 95% confidence intervals (CIs) were calculated for binary outcomes. In the case of LOH, standardized mean difference with 95% CI was calculated to compare mean data. We used the conversion method by Hozo et al[40] because only the median and interquartile range were provided in some studies.[31,35,37] All analyses were 2-tailed, with an α value of 0.05.

Heterogeneity was tested using Cochrane Q and I^2 statistics. Based on the *Cochrane Handbook*, $I^2 = 100\% \times (Q - df)/Q$ represents the magnitude of the heterogeneity (moderate, 30%–60%; substantial, 50%–90%; considerable, 75%–100%).[41]

The results from 4 or more studies were displayed graphically using forest plots. These outcomes are mortality, LOH, and complications. Results were also weighted based on the number of patients studied in the articles. To assess required information size and to estimate the robustness of our conclusions, we conducted a trial sequential analysis (TSA; with TSA tool from Copenhagen Trial Unit, Center for Clinical Intervention Research,

TABLE 1. Description of the Studies Included in the Meta-analysis

Study	Country	Study Type	Years of Study	Group	Sample Size	Age,* y
Huh et al, 2016[36]	Korea	Retrospective	2013–2015	DM	54	62.5
				Non-DM	147	58.3
Kikuta et al, 2015[30]	Japan	Retrospective	2007	DM	250	60.3
				Non-DM	1704	59.1
Kumar et al, 2015[33]	India	Retrospective	2011–2012	DM	34	—
				Non-DM	48	—
Méndez-Bailón et al, 2015[37]	Spain	Retrospective	2001–2011	DM	42,009	69.6
				Non-DM	240,340	62.1
Mole et al, 2016[34]	Scotland	Retrospective	2009–2012	DM	398	—
				Non-DM	1655	—
Nawaz et al, 2015[35]	United States	Retrospective/prospective	1996–2005	DM	1349	63
				Non-DM	6050	56
Shen et al, 2012[31]	Taiwan	Retrospective	2000–2009	DM	18,990	58
				Non-DM	37,980	58
Shen et al, 2012[32]	Taiwan	Prospective	No data	DM	2165	—
				Non-DM	1389	—
Zhao et al, 2012[38]	China	Retrospective	2009–2010	DM	40	57.2
				Non-DM	278	44.3

*Data expressed as either mean or median.

Denmark; version 0.9 beta, www.ctu.dk/tsa) and a sensitivity analysis. The required information size calculation was based on the assumption of a 10% relative risk reduction, and we adjusted all analysis for heterogeneity (diversity adjustment). The TSA monitoring boundaries were built based on a risk for a type I error of 5% and a type II error of 20%. If a TSA monitoring boundary is crossed with a *Z*-curve before the required information size is reached, robust evidence might have been confirmed and further trials are unnecessary. Therefore, more trials are needed in this field. With sensitivity analysis, we can assess whether altering any of the assumptions may lead to different final interpretations or conclusions.[42]

Quality of Studies and Risk of Bias

Because of the low number of articles, publication bias was obtained by visual inspection of the funnel plots. The Newcastle-Ottawa scale[43] was used for a quality assessment of nonrandomized cohort studies. The selection, comparability, and outcome data were assessed with the star system based on 7 items (Supplementary Tables 3–4, http://links.lww.com/MPA/A663): high-quality items carrying a low risk of bias were assigned one star, whereas low-quality items carrying a high or unknown risk of bias received no stars. Selection consisted of 4 items, with articles earning 2 stars for comparability and only adequacy of follow-up being rated at outcome. Assessment of outcome and length of follow-up were not rated because most of the articles were retrospective. We assigned a star for responsiveness of study population if all of the AP patients with or without DM were included, but no stars were given whenever selection criteria were applied. Low risk of bias was assessed if AP diagnosis was ascertained by 2 of 3 criteria (elevation of serum amylase and/or lipase activity at least 3 times higher than the upper normal limit, presence of abdominal pain, and inflammation detected with abdominal ultrasound and/or computed tomography) and if the standard definition of preexisting DM was applied, whereas the inclusion of newly diagnosed DM based on elevated HbA1c was also acceptable.[44] Diabetes mellitus and non-DM patients were compared based on age and body mass index because the negative influence of obesity is well known in AP patients.[45] If there was a follow-up, the adequate number of patients was screened for complications.

RESULTS

Study Selection

Database searches produced a total of 1417 articles (Embase, 759; PubMed, 590; Cochrane, 68). The flow chart diagram (Fig. 1) shows the strategy for article selection. Studies used in our meta-analysis were dated from 1948 to March 2017. After removal of duplicates, 1119 unique records remained. Following initial screening based on titles and abstracts, case reports and records with data on children were excluded; 52 articles were finally retrieved and screened. A further 43 articles were excluded: 34 because the main outcome was the risk of development of AP, 5 because of the inappropriate classification of values (there were no DM and non-DM groups), 1 by reason of missing numerical outcome data, 2 with only late outcome data (pancreatic exocrine or endocrine insufficiency), and 1 in which not all of the patients had AP. The remaining 9[30–38] articles were included in the meta-analysis (Table 1). They consisted of 354,880 patients, 65,289 of whom had preexisting DM as a comorbidity.

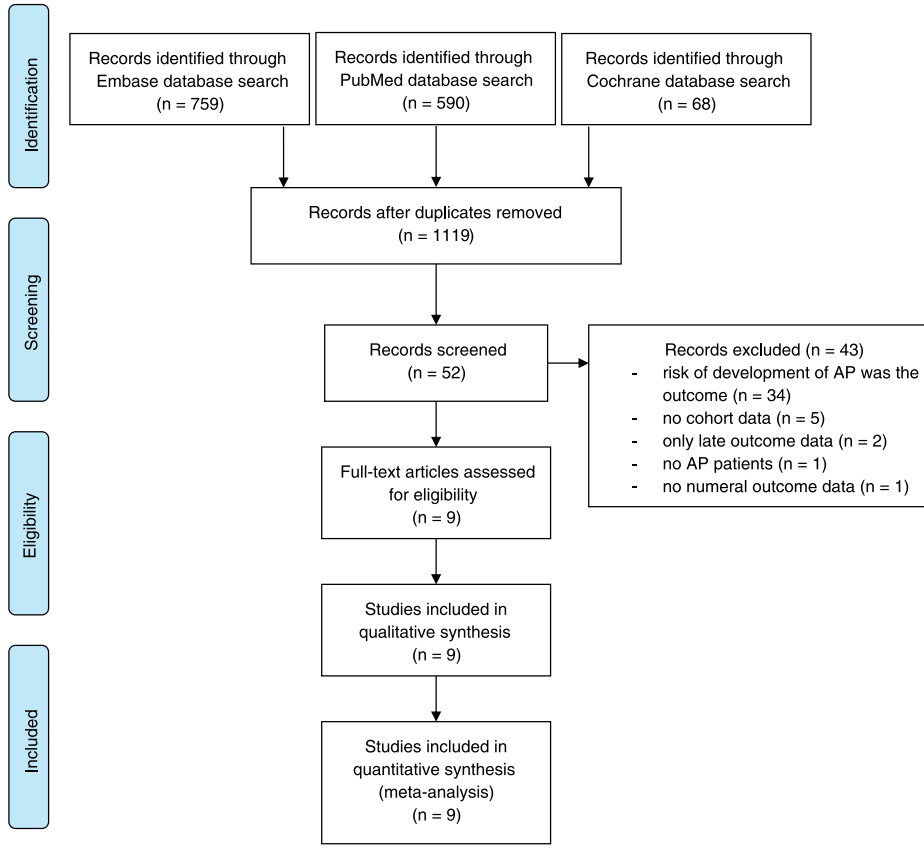

FIGURE 1. Flowchart for the study selection procedure.

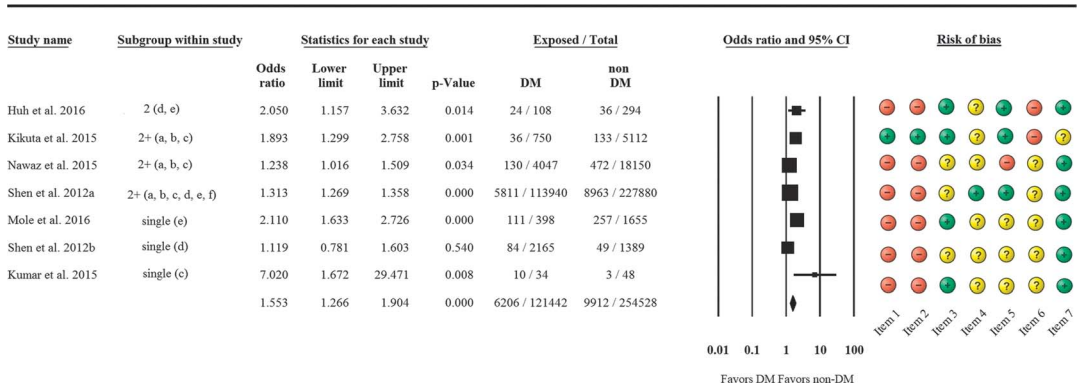

FIGURE 2. Forest plot representing the differences in complications in DM and non-DM patients suffering from AP. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% CIs. Single, only 1 complication is available; 2+, more complications are available; a, cardiovascular; b, respiratory; c, renal; d, local; e, intensive care unit admission; f, neurological.

Complications

The rate of complications in the 2 AP groups was analyzed first. Overall, based on 7 articles, more complications were seen in DM patients than in non-DM patients (OR, 1.553 [95% CI, 1.266–1.904]; $P < 0.001$) (Fig. 2).

A subgroup analysis was conducted to detect which types of complications are most frequent in DM. In the case of preexisting DM, significantly more ICU admissions (OR, 1.799 [95% CI, 1.442–2.243]; $P < 0.001$) and renal failure (OR, 1.585 [95% CI, 1.278–1.966]; $P < 0.001$) were seen than in non-DM patients. Diabetic patients more often develop local complications (OR, 1.276 [95% CI, 0.991–1.643]; $P = 0.059$), but the difference did not reach statistical significance. No differences were found in cardiovascular (OR, 0.942 [95% CI, 0.722–1.23]; $P = 0.661$), neurological, and respiratory complications (OR, 1.060 [95% CI, 0.833–1.349]; $P = 0.636$) (Fig. 3).

Mortality and LOH

Among the 9 studies, only 6 included the mortality data for AP patients. A tendency of higher AP mortality was observed in DM patients as compared with non-DM patients (OR, 1.265 [95% CI, 0.964–1.659]; $P = 0.090$) (Fig. 4). Length of hospitalization was longer in DM patients than in non-DM patients based on 5 articles (standardized mean difference, 0.217 [95% CI, 0.075–0.360]; $P = 0.003$) (Fig. 5).

Heterogeneity and Quality Assessment of Data

High heterogeneity was detected for overall complications ($Q = 25.12$; DF = 6; $I^2 = 76.11\%$; $P < 0.001$), renal failure ($Q = 10.32$; DF = 3; $I^2 = 70.96\%$; $P = 0.016$), mortality ($Q = 49.2$; DF = 5; $I^2 = 89.84\%$; $P < 0.001$) and LOH ($Q = 414.74$; DF = 4; $I^2 = 99.03\%$; $P < 0.001$), whereas lower heterogeneity was observed for ICU admission ($Q = 4.43$; DF = 2; $I^2 = 54.84\%$; $P = 0.11$) and local complications ($Q = 1.77$; DF = 2; $I^2 = 0\%$; $P = 0.41$). To evaluate publication bias, we only made a visual assessment of the funnel plot (Supplementary Fig. 1, http://links.lww.com/MPA/A677) because we were only able to include 9 studies in our meta-analysis. According to the *Cochrane Handbook*,[41] "tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer

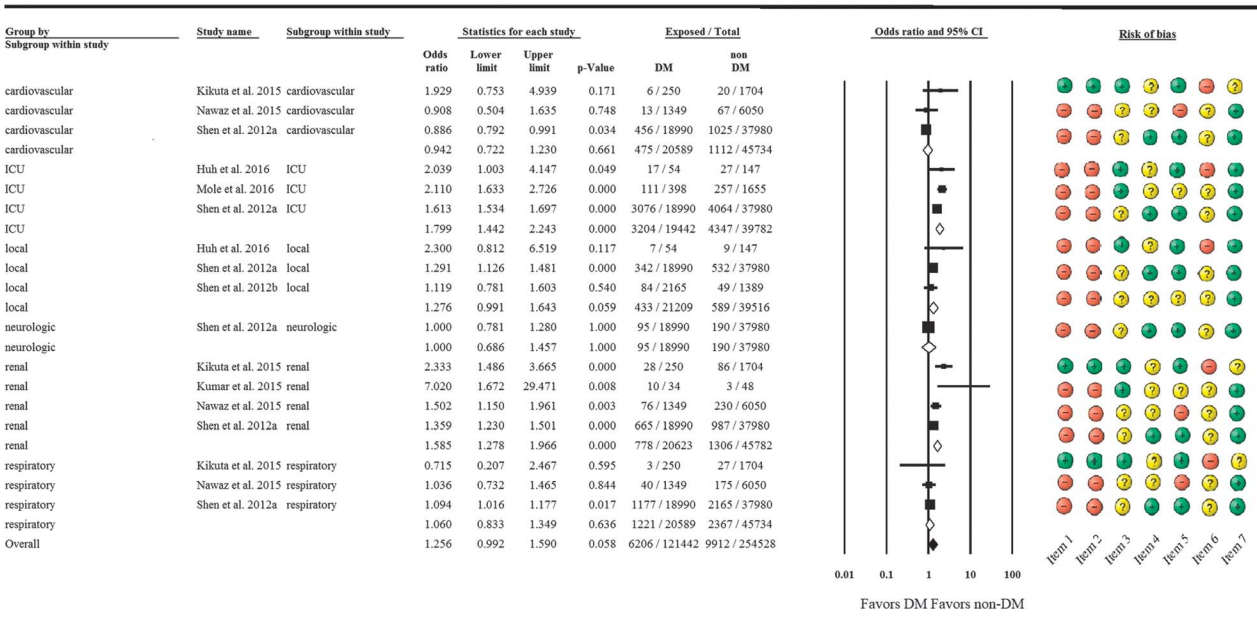

FIGURE 3. Forest plot representing detailed differences in several types of complications in DM and non-DM patients suffering from AP. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% CIs.

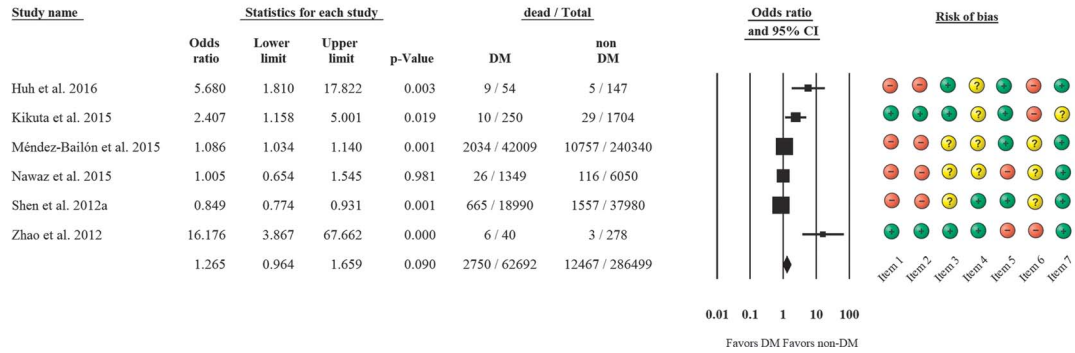

FIGURE 4. Forest plot representing the differences in mortality in DM and non-DM patients suffering from AP. Size of squares for risk ratio reflects weight of trial in pooled analysis. Horizontal bars represent 95% CIs.

studies the power of the tests is too low to distinguish chance from real asymmetry." Articles received between 1 and 5 stars out of the maximum 7 stars on the Newcastle-Ottawa scale (Supplementary Table 4, http://links.lww.com/MPA/A663). A high risk of bias was identified in terms of the representativeness of the study population because AP patients were selected in most of the articles (Supplementary Fig. 2, http://links.lww.com/MPA/A678). The percentage of unclear risk of bias was 77.8% in the presence of outcome of interest (Supplementary Fig. 2, http://links.lww.com/MPA/A678), but cardiovascular, renal, and respiratory complications were available in only 3 or 4 articles. Body mass index data were available in only 3 articles, but unfortunately, a statistical difference was observed between DM and non-DM groups. Two articles earned only 1 star,[32,35] whereas 1 article received 5 stars[38] (Supplementary Table 4, http://links.lww.com/MPA/A663).

Sensitivity analysis showed no significant difference in overall and detailed complications and LOH (Supplementary Figs. 3A, B, D, http://links.lww.com/MPA/A679), whereas if we remove the Méndez-Bailon[37] and Shen et al[31] articles with respect to mortality, OR for mortality would change significantly from pooled OR (2.152 [95% CI, 1.063–4.358], $P = 0.033$ and 2.157 [95% CI, 1.165; 3.995], $P = 0.014$, respectively) (Supplementary Fig. 3C, http://links.lww.com/MPA/A679). Both articles involve a high number of patients and a longer follow-up time, but both articles contain data on a large patient population. We therefore included them in our meta-analysis.

Trial sequential analysis showed that in combinations and mortality the information size to achieve is 2,903,700, and these studies do not reach this yet (Supplementary Figs. 4A, B, http://links.lww.com/MPA/A680). With regard to LOH, studies reached the appropriate information size (301,416) (Supplementary Fig. 4C, http://links.lww.com/MPA/A680).

DISCUSSION AND CONCLUSIONS

In this meta-analysis, we investigated the influence of preexisting DM on different outcome parameters in AP patients. With regard to overall complications, we found significantly more complications in DM groups than in non-DM groups (Fig. 2), and higher rates of renal failure and ICU admission were also observed (Fig. 3). One quarter to half of the patients diagnosed with DM might develop chronic kidney disease, thus increasing mortality of DM.[46] The development of renal failure determines the severity of AP according to the revised 2012 Atlanta Classification,[3] and it raises the mortality of AP.[47] The mechanism for renal failure during AP is not yet completely understood, but it has been shown that injury due to inflammatory mediators, cytokines, transcription factors, microcirculation changes, and apoptosis are important pathogenic factors.[48] Development of renal failure increased the mortality of AP, suggesting that it has detrimental effects on patients with preexisting DM. The data in our meta-analysis indicated a tendency of higher mortality in DM patients (Fig. 4). It must be noted that there are data that contradict our findings. Intensive care unit mortality only grew significantly with higher mean blood glucose concentration in non-DM patients but not in DM patients.[14,49] For example, Graham et al[50] showed that critically ill patients with DM do not experience higher mortality compared with that seen in patients without DM. This may be explained with the beneficial antioxidant and anti-inflammatory effects of exogenous insulin used for treating hyperglycemia in

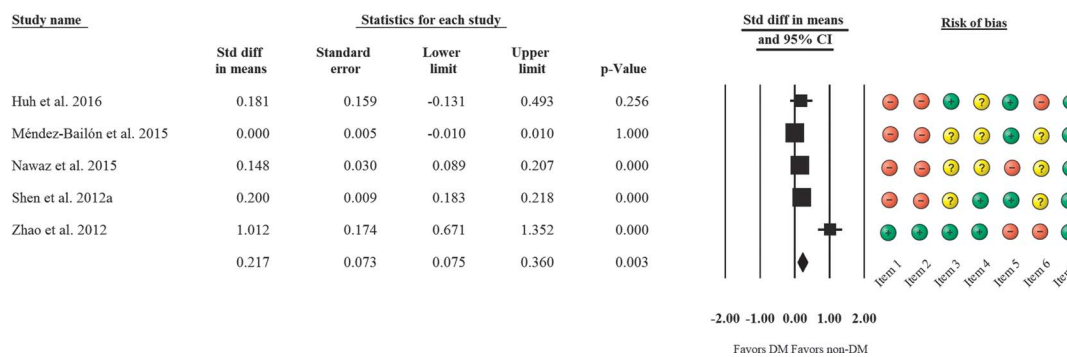

FIGURE 5. Forest plot representing the differences in LOH in DM and non-DM patients suffering from AP. Size of squares for the difference in standardized mean values reflects weight of trial in pooled analysis. Horizontal bars represent 95% CIs.

DM.[51,52] Insulin acts on the suppression of innate immune mechanisms and transcription factors NF-κB and Egr-1.[52] With regard to the local complications in our analyses, DM patients tend to develop local complications more often. This is most probably due to damage to the endocrine-exocrine axis, which was discussed in detail in the background section.

Based on pooled data, diabetic AP patients spend more time in hospital (Fig. 5). This can be explained by the more intense systemic inflammatory response, more frequent complications, slower recovery, and settlement of glucose homeostasis in DM patients. The OR calculated for mortality and LOH data in Zhao et al[38] differ from those in the other studies. This is clear from the mortality and LOH data, but we did not remove it because this article received the highest points on the Newcastle-Ottawa scale and the sensitivity analysis showed no difference. In cases of cardiovascular and respiratory complications, no difference was observed based on diabetic status.

Several studies have demonstrated that obesity may worsen the clinical outcome of AP.[45,53,54] Diabetes mellitus patients tend to have higher body mass index, but unfortunately this data was only represented in a few articles and therefore was not suitable for data analysis.

There are several limitations of this study; therefore, the results of this meta-analysis should be regarded with caution. The greatest limitation is the low number of eligible articles included, thus causing higher heterogeneity. Second, the low amount of extracted data causes further difficulties. In addition, this meta-analysis includes mostly retrospective cohort studies. Five of 9 articles report patients from East Asia (Taiwan, Japan, Korea, and China), and only 2 present data on patients with severe AP. The Newcastle-Ottawa scale star count is unfortunately low because the data were incomplete. Trial sequential analysis showed that no sufficient data are available on this topic and further investigations are needed to show the connection between DM and complications of AP. However, despite the limitations, a notable advantage of our analysis is that it covers articles with data on patients from the last 20 years.

In summary, our meta-analysis highlights the crucial importance of the diagnosis of DM in AP patients. It is therefore highly recommended that a diagnosis be made by measuring fasting glucose and HbA1c levels on admission. The increased risk for renal failure warrants more frequent measurements of renal function parameters in AP patients also suffering from DM. Nevertheless, the high frequency of the cooccurrence of DM and AP patients suggests that further prospective high-quality cohort studies are necessary to understand the true link between AP and preexisting DM. First, an observational clinical trial would help us to understand the differences between the effects of (1) untreated preexisting diabetes with high HbA1c level and (2) well controlled, previously diagnosed diabetes. Second, the local mechanisms behind the harmful effects of preexisting diabetes need in depth scrutiny. Therefore, another trial should be performed in which the levels of insulin, C-peptide, and glucagon are measured in patients with AP and DM. It is needless to say that further interventional studies should be performed to identify the best treatment options of diabetes during AP.

In conclusion, our systematic review and meta-analysis clearly shows that preexisting DM negatively influences AP outcomes by raising the incidence of renal failure, ICU admission, and LOH and leads to a tendency of higher mortality.

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