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Stem Cell-Derived Extracellular Vesicles for Acute Pancreatitis: a Systematic Review and Meta-analysis of Preclinical Studies

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Abstract

Background Several studies have reported the effectiveness of stem cell-derived extracellular vesicles (SC-EVs) in disease treatment. However, the efficacy of SC-EVs for severe acute pancreatitis (SAP) remains uncertain. This systematic review aimed to analyze and evaluate the effect of SC-EVs in the treatment of SAP in animal models by summarizing data from published studies.

Methods We searched Pubmed, Embase, and Web of Science databases to identify preclinical studies investigating the therapeutic effect of SC-EVs on SAP. The primary outcome was the histopathological scores of pancreatic tissues, including inflammation, edema, and necrosis. Other outcome measures included levels of amylase, IL-6, IL-10, and TNF-α. Eligible studies were selected based on the inclusion and exclusion criteria. SYRCLE checklist was adopted to assess the quality and bias risks of included studies. Mean differences and 95% confidence intervals were calculated using the inverse variance method with a random effects model. All statistical analyses were performed using RevMan 5.3 software.

Results A total of 8 studies including 126 animals were included. The results of meta-analysis revealed that SC-EVs treatment significantly reduced pancreatic histopathologic scores (total score: MD = -5.17, 95% CI: -5.79, -4.55; inflammation score: MD = -1.44, 95% CI: -1.70, -1.19; edema score: MD = -1.42, 95% CI: -1.75, -1.09; necrosis score: MD = -1.42, 95% CI: -1.80, -1.04), inhibited pro-inflammatory factor release (IL-6: SMD = -3.20, 95% CI: -4.51, -1.88; TNF-α SMD = -5.18, 95% CI: -6.96, -3.40), and enhancing the release of anti-inflammatory factors (IL-10 SMD = 4.15, 95% CI: 2.49, 5.81). Further subgroup analyses displayed SC-EVs treatment obviously attenuated animal pancreatic pathologic injury in traumatic pancreatitis and drug-induced acute pancreatitis, and the effect of SC-EVs to inhibit TNF-α secretion in the drug-induced SAP model was correlated with the dose of SC-EVs injection.

Conclusions This meta-analysis displayed that SC-EVs were correlated with SAP injury alleviation and pancreas function reservation. Research into the treatment of SAP with SC-EVs is still in its early stage, necessitating further comprehensive investigations in the future to elucidate the therapeutic mechanisms of SC-EVs and their potential application in SAP.

Keywords Stem cells · Extracellular vesicles · Severe acute pancreatitis · Preclinical study

Introduction

Acute pancreatitis (AP) is characterized by inflammation of the pancreas. While the majority of cases are mild and resolve spontaneously, approximately 15–20% of individuals with AP develop localized and systemic complications, leading to multi-organ failure and even mortality [1, 2]. Despite advancements in multidisciplinary care and individualized treatment strategies, mortality rates for severe acute pancreatitis (SAP) have remained largely unchanged [3, 4]. Current treatments for SAP are quite limited, therefore, there is a desperate need to investigate novel therapeutic strategies to improve SAP prognosis.

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Mesenchymal stem cells (MSCs) have become an important choice for cell therapy due to their availability, abundant sources, and low tumorigenicity [5]. Exogenously infused MSCs exert their therapeutic effects primarily by migrating to damaged tissues and engaging with resident cells, releasing anti-inflammatory cytokines, growth factors, chemokines, etc [6]. Studies have shown that MSC therapy for pancreatitis significantly improved pancreatic injury and alleviated inflammatory responses [7, 8]. However, challenges like the heterogeneity of cell sources, low survival rates, and cell infusion-related toxicity limit the application of MSCs [9].

Extracellular vesicles (EVs) are secreted by various kinds of cell types, dividing into exosomes, microvesicles, and apoptotic vesicles according to diameters [10]. Studies have reported that the beneficial effects of MSCs are mainly attributed to their paracrine ability. EVs, as the major paracrine components, serve as the key mediator of the interaction between stem cells and their targets [11, 12]. Preclinical studies have shown that stem cell-derived EVs (SC-EVs) demonstrate therapeutic efficacy comparable to MSCs, offering advantages such as small size, high safety, and targeted delivery. EVs derived from different MSC sources exhibit both commonality and specificity in biological functions, presenting potential probability for precision treatments [13, 14]. SC-EVs treatments have shown positive effects on pancreatitis-associated lung injury and myocardial injury [15, 16]. Although several preclinical studies have reported the effect of SC-EVs on SAP treatment, there is still a lack of a unified conclusion. This meta-analysis is to provide the latest evidence of the effectiveness of SC-EVs in SAP treatment, offering a theoretical foundation for their application in the treatment of SAP patients.

Methods

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17].

Search Strategy

We completed a comprehensive review of studies related to SC-EVs treatment on SAP in Pubmed, Embase, and Web of Science databases till April 18, 2024. Manual search was done to ensure that all relevant studies were collected. Search strategy was based on a strategy of MESH or Emtree terms (stem cell, extracellular vesicles, pancreatitis) and free terms. Specific search formulas were presented in Supplematerial S1.

Study Selection

After removing duplicate references and initially excluding obviously irrelevant studies by title and abstract, the remaining studies were reviewed in detail and rigorously screened based on the inclusion and exclusion criteria. Inclusion criteria: (1) evaluated the therapeutic efficacy of EVs treatment of SAP animal model; (2) provided detailed methodology on the extraction and identification of EVs; (3) studies reported HE pathology scores of pancreas; (4) written in English. Exclusion criteria: (1) studies with data that could not be extracted and incomplete data; (2) studies that lacked EVs solvent carrier control; (3) EVs were not directly used for treatment; (4) studies that lacked unmodified EVs; and (4) non-original studies (containing reviews, editorials, conference abstracts, other meta-analyses, etc.). Two authors (YHH, MLY) performed study selection independently, and any discrepancies were resolved with discussion with the third author (JL).

Data Extraction

The following information was extracted from included studies: (1) general information: first author, year of publication, country, and region; (2) EVs characteristics: source, methods of extraction and identification; (3) modeling: animal type, sex, modeling procedure, dose and route of EVs administration, observation time; and (4) outcomes: HE pathology scores, amylase, cytokines: IL-6, TNF-α, IL-10. For results reported at multiple time points, only the last time point was extracted. Numerical data not directly provided were obtained using Engauge Digitizer 11.1. For means ± standard deviation not directly provided, sample sizes ≤ 60, standard deviations were calculated from sample sizes, means, and 95% confidence intervals according to the formula in the Cochrane Handbook. Data extraction was performed independently by two authors (YHH, MLY), and data with differences < 10% were averaged, and data with > 10% were discussed and resolved with a third author (JL). More information was obtained by contacting the authors of the paper, and studies for which data were ultimately unavailable were excluded.

Risk of Bias Evaluation

As a preclinical animal model study, the risk of bias was assessed according to the Systematic Review Center for Laboratory Animal Experiments (SYRCLE) [18], which included random sequence generation bias, groups baseline bias, allocation concealed bias, animals randomly housed bias, caregiver blinding bias, random selection bias, outcome assessing bias, incomplete data bias, outcome

selection bias and free from other bias (Table S1). Two authors (YHH, MLY) performed the risk assessment independently and resolved the discrepancies by discussion with a third author (JL).

Statistical Analysis

The study was conducted using Review Manager 5.3. Continuous variables were compared by mean difference (MD) or standardized mean difference (SMD) and 95% confidence interval (CI). A random-effects model was employed for meta-analysis to calculate the mean effect of changes in HE pathology scores, amylase, and inflammatory factors between the SC-EVs and vehicles groups. Funnel plots were applied to test publication bias in the study. I^2 tests were used to measure heterogeneity of outcome measures. When significant heterogeneity existed, subgroup analyses were conducted to determine the source of heterogeneity, and individual studies were excluded on a case-by-case basis for sensitivity analyses. $P<0.05$ (two-sided) were considered statistically significant.

Results

Characteristics of Included Studies

A total of 321 studies were extracted from the Pubmed, Embase, and Web of Science databases. 50 duplicates were excluded and preliminary exclusions were made according to the titles and abstracts of the studies. The remaining 39 studies were reviewed thoroughly, and a total of 8 articles were included in this meta-analysis after strictly screening according to the inclusion and exclusion criteria (Fig. 1) [19–26]. The specific information of included studies is summarized in Table 1.

9 experiments were included in the 8 studies, containing a total of 126 animals. Animal experiments primarily utilized SD rats ($n=7$), with C57BL/6 J mice ($n=2$) also employed. Human umbilical vein MSCs were the main source of exosomes ($n=6$), while others chose mouse hair follicle MSCs ($n=2$) and rat bone marrow MSCs ($n=1$). EVs were extracted by ultracentrifugation ($n=9$). The identification of EVs included size, morphology, and protein markers. Exosome size was analyzed primarily by Nanoparticle Tracking Analysis (NTA), and morphology was detected via electron microscopy, supplemented by western blot quantification of protein markers ($n=6$). Tail vein injection was the preferred route of EVs administration ($n=8$), followed by intraperitoneal injection ($n=1$). Administration timing was predominantly 6–8 h post-SAP induction ($n=5$), with some instances of immediate ($n=2$), 2-hour ($n=1$), and 12-hour ($n=1$) post-induction. Notably, certain studies performed modifications on parental stem cells of EVs ($n=3$). SAP models were mainly induced by retrograde injection of sodium taurocholate solution (NaT) through the common biliopancreatic duct ($n=4$), followed by intraperitoneal injection of caerulein ($n=2$), and traumatic extrusion ($n=3$). Observation time points primarily included 24 h ($n=5$), followed by 72 h ($n=3$), and 48 h ($n=1$) post-SAP induction.

Risk of Bias Assessment

All included studies indicated randomization in the allocation of animals without further details, resulting in the "unclear" risk of bias in sequence generation. Notably, randomization occurred prior to modeling without explicit details in included studies, and allocation concealment was not adequately illustrated. All studies documented the animal randomization, thus excluding the area of "high" risk of group randomization. Most studies emphasized blinding during HE pathology assessment ($n=8$), ensuring a "low" risk of bias in outcome analysis. None of the studies provided records of sample size estimates. A comprehensive count of the number of animals was performed in the results section, ensuring a "low" risk of attrition and reporting of studies. In addition, the risk of bias for the other dimensions was consistently "unclear" for all included studies. Overall, the cumulative assessment suggested a moderate-quality study design (Table S1).

EVs Treatment Improved Histopathologic Damage of Pancreas in SAP

A total of 126 animals were assessed for HE pathology of pancreatic tissue after SAP modeling. 3 experiments involving 40 animals utilized the HE composite score, revealing a significant improvement in pancreatic pathology following SC-EVs treatment (MD = −5.17, 95% CI: −5.79, −4.55, $p<0.00001$, $Tau^2=0.10$, $I^2=31\%$). Moreover, 6 trials examined inflammation, edema and necrosis subscores, with EVs treatment significantly ameliorating pancreatic inflammation (MD = −1.44, 95% CI: −1.70, −1.19, $p<0.00001$, $Tau^2=0.06$, $I^2=83\%$), edema (MD = −1.42, 95% CI: −1.75, −1.09, $p<0.00001$, $Tau^2=0.12$, $I^2=90\%$) and necrosis (MD = −1.42, 95% CI: −1.80, −1.04, $p<0.00001$, $Tau^2=0.19$, $I^2=92\%$) (Fig. 2). In addition, all 9 trials evaluated changes in serum amylase pre- and post-EVs intervention, demonstrating a significant reduction in serum amylase levels after EVs treatment (SMD = −3.24, 95% CI: −4.38, −2.10, $p<0.00001$, $Tau^2=1.97$, $I^2=73\%$) (Fig. S1).

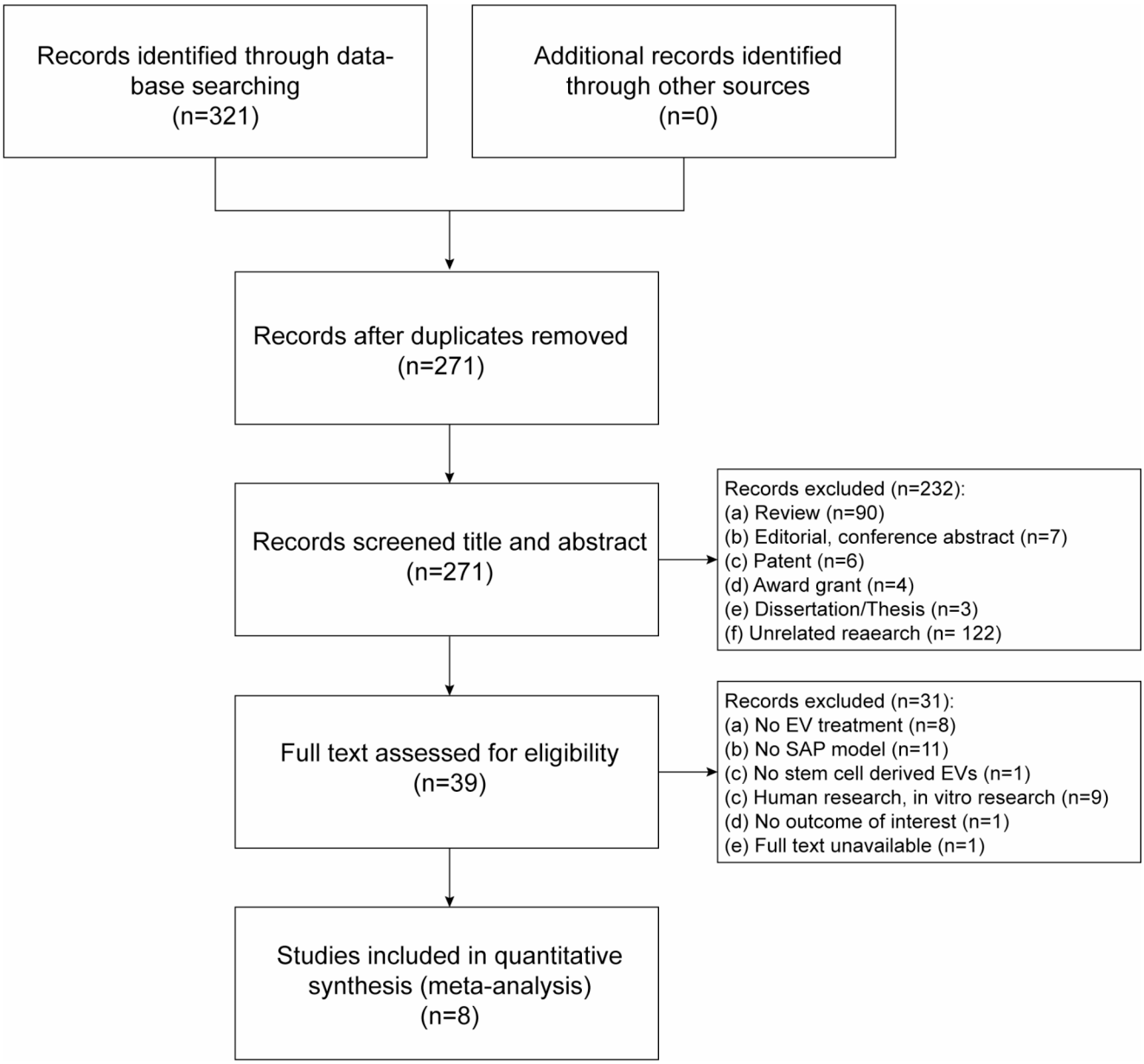

Fig. 1 PRISMA flow diagram

EVs Treatment Decreased Pro-inflammatory Factor Release and Increased Anti-inflammatory Factor Secretion

A total of 9 experiments counted the serum expression of IL-6 after SAP modeling in 126 animals as shown in Fig. 3a, revealing a reduction in IL-6 release following EVs treatment (SMD = −3.20, 95% CI: −4.51, −1.88, $p<0.00001$, $Tau^2=3.00$, $I^2=81\%$). Additionally, 8 experiments indicated that SC-EVs treatment attenuated TNF-α release (SMD = −5.18, 95% CI: −6.96, −3.40, $p<0.0001$, $Tau^2=4.81$, I^2 = 77%) (Fig. 3b). 8 trials reported that SC-EVs treatment promoted IL-10 secretion (SMD = 4.15, 95% CI: 2.49, 5.81, $p<0.00001$, $Tau^2 = 4.42$; $I^2 = 83\%$) (Fig. 3c).

Subgroup and Sensitivity Analyses

Subgroup analyses were conducted to investigate sources of heterogeneity. Notably, in pancreatic inflammation, edema, and necrosis scores, heterogeneity was significantly affected by SAP modeling. SC-EVs treatment in drug induced SAP model significantly improved pancreatic inflammation (MD = −0.86, 95% CI: −1.17, −0.54, $p<0.00001$, $Tau^2 = 0.00$, $I^2 = 0\%$) (Fig. 4a), edema (MD = −0.64, 95% CI: −0.96, −0.31, $p=0.0001$, $Tau^2 = 0.00$, and $I^2 = 0\%$) (Fig. 4b) and

Table 1 Summary of studies included in the systematic review

Study	Species/age/gender/weight	Number	SAP model	Specific modeling	Characteristics and injection of EVs					HE score evaluation	Duration
					Source	Diameter (nm)	Route	Dose	Time-point		
Hu 2023 [19]	SD rat, 6w, M,	16	Drug induced	NaT injected into the common biliopancreatic duct retrogradely	hUC-MSCs	100–400	IV	1 mg/kg	6 h after SAP	Blinded	72 h
Han 2022 [20]	SD rat, 200–250 g	20	Traumatic squeeze	Percuss and squeeze pancreatic tissue	hUC-MSCs	160.2	IV	10 μg/100 g	Immediately	Blinded	24 h
Li 2022a [21]	C57BL/6J mouse, 4-6w, M, 22–25 g	12	Drug induced	Caerulein injected intraperitoneally	Mouse HF-MSCs	50–200	IV	200 μg	8 h after SAP	NA	24 h
Li 2022b [21]	C57BL/6J mouse, 4-6w, M, 22–25 g	12	Drug induced	Caerulein injected intraperitoneally	Mouse HF-MSCs	50–200	IP	200 μg	8 h after SAP	NA	24 h
Ma 2023 [22]	SD rat, 6w, 280–200 g	12	Drug induced	NaT injected into the common biliopancreatic duct retrogradely	hUC-MSCs	153.1–159.1	IV	400 μg	6 h after SAP	Blinded	72 h
Xie 2023 [23]	SD rat, 6w, M, 180~200 g	12	Drug induced	NaT injected into the common biliopancreatic duct retrogradely	hUC-MSCs	149.6–150.5	IV	400 μg	6 h after SAP	Blinded	72 h
Yin 2016 [24]	SD rat, F	12	Drug induced	NaT injected into the common biliopancreatic duct retrogradely	Rat BMSCs	NA	IV	1000 μg	2 h after SAP	Blinded	12 h, 24 h, 48 h
Zhao 2022 [25]	SD rat, M	16	Traumatic squeeze	Percuss and squeeze pancreatic tissue	hUC-MSCs	80–150	IV	10 μg/100 g	12 h after SAP	Blinded	24 h
Zhao 2024 [26]	SD rat, 200–250 g	20	Traumatic squeeze	Percuss and squeeze pancreatic tissue	hUC-MSCs	78.51 nm	IV	10 μg/100 g	Immediately	Blinded	24 h

NaT Na-taurocholate, *hUC-MSCs* human umbilical cord-derived mesenchymal stem cells, *HF-MSCs* hair follicle-derived MSCs, *BMSCs* bone marrow mesenchymal stem cells, *IV* Intravenous injection, *IP* intraperitoneal injection, *NA* not applicable

pancreatic necrosis (MD = −0.77, 95% CI: −1.10, −0.44, $p<0.00001$, $Tau^2 = 0.02$, $I^2 = 22\%$) (Fig. 4c). Similarly, in traumatic pancreatitis (TP) models, SC-EVs treatment alleviated pancreatic inflammation (MD = −1.44, 95% CI: −1.70, −1.19, $p<0.00001$, $Tau^2 = 0.00$, $I^2 = 42\%$) (Fig. 4a), edema (MD = −1.79, 95% CI: −1.88, −1.69, $p=0.0001$, $Tau^2 = 0.00$, $I^2 = 0\%$) (Fig. 4b) and necrosis (MD = −1.93, 95% CI: −2.06, −1.80, $p<0.00001$, $Tau^2 = 0.00$, $I^2 = 33\%$) (Fig. 4c). Heterogeneity in TNF-α expression was significantly influenced by the type of raw data collected and the injection dose of SC-EVs (Table S2). However, no significant effects of animal type, sex, modeling, or injection

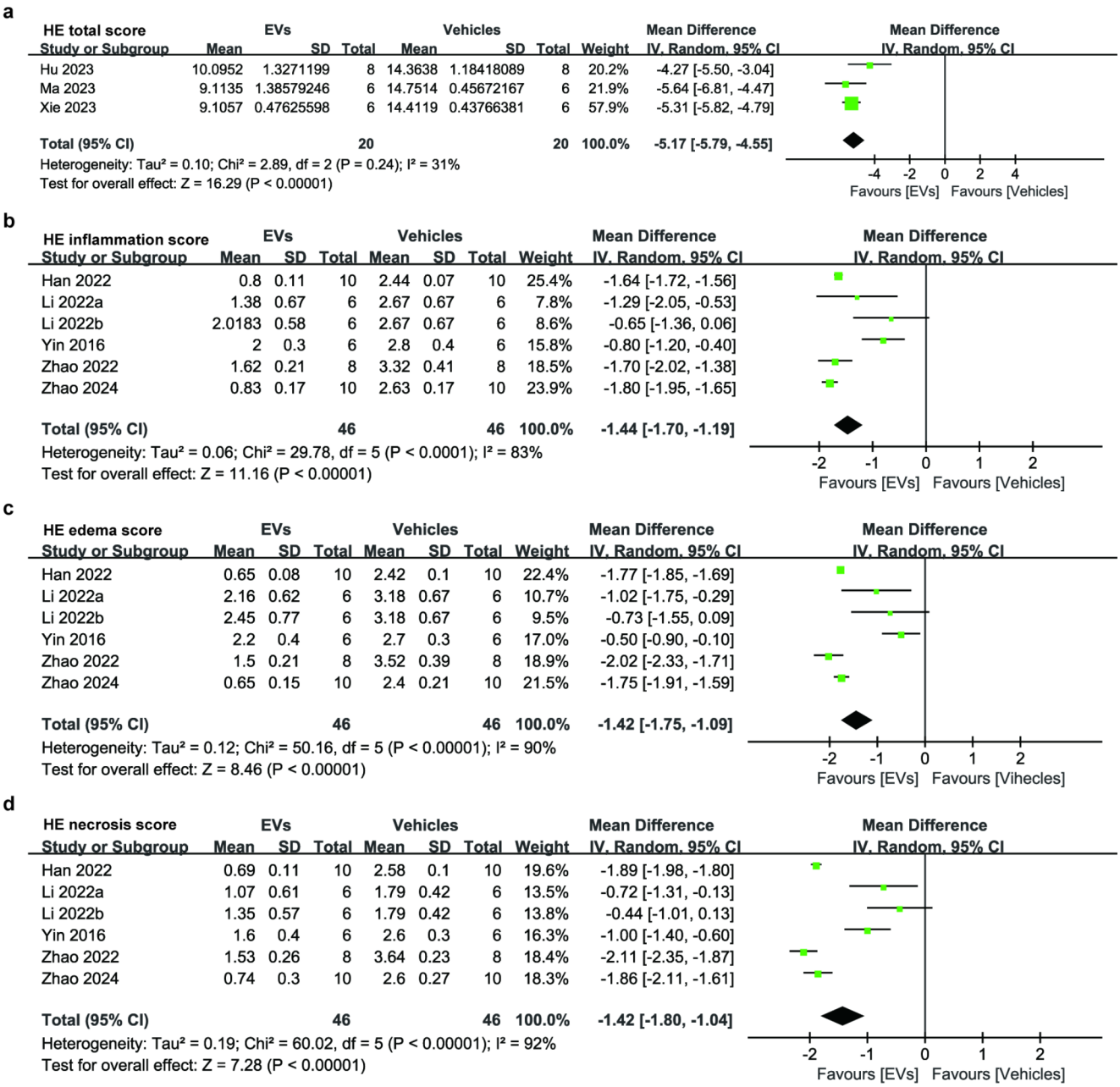

Fig. 2 Forest plots of the effect of EVs on the HE score of pancreas. (**a**) the total score of HE staining. (**b**) the inflammation score. (**c**) the edema score. (**d**) the necrosis score

time on SC-EVs' efficacy were observed. Sensitivity analyses were conducted by excluding studies individually and recalculating the pooled effect size, revealing no significant improvement in between-study heterogeneity, suggesting the absence of significant sources of heterogeneity.

Risk of Publication Bias

Possible publication bias in this study was examined by funnel plot. No significant publication bias was found regarding the HE pathologic tissue scores (total score, inflammation, edema, and necrosis) (Figure S2).

Discussion

A meta-analysis comprising 8 preclinical studies investigated the therapeutic potential of stem cell-derived EVs in severe acute pancreatitis treatment. Our findings indicated that EVs treatment significantly reduced pancreatic histopathologic injury, inflammation, edema, necrosis, and

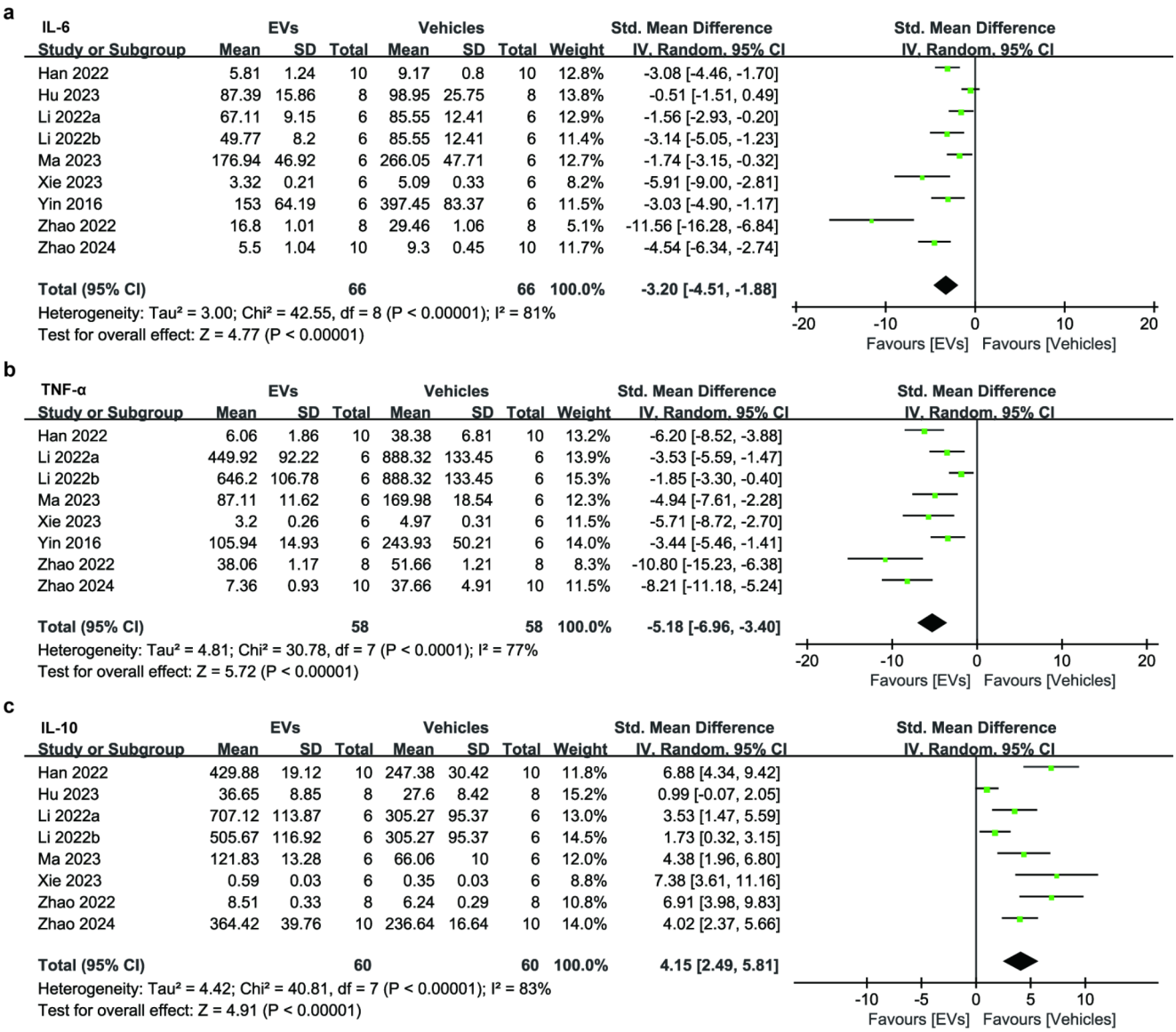

Fig. 3 Forest plots of the effect of EVs on the pro- and anti-inflammatory factors secretion after SAP. (**a**) IL-6. (**b**) TNF-α. (**c**) IL-10

pancreatic amylase expression compared to controls. This therapeutic efficacy of EVs may be attributed to their ability to suppress inflammatory factors IL-6 and TNF-α, while promoting the secretion of IL-10.

Study Bias and Heterogeneity

This study thoroughly considered the potential biases and heterogeneity within the included studies. Assessment of publication bias risk using the SYRCLE scale revealed that all studies employed subgrouping before intervention without addressing allocation concealment implementation. Additionally, the lack of specific methodological descriptions, such as sample size estimation formulas, hindered certain assessments, underscoring the need for improved methodological transparency in future preclinical studies of EVs treatment. Although a high degree of heterogeneity was observed in the results of amylase and inflammatory factors, likely stemming from various factors including EVs source, implementation method, and treatment approach, the overall consistency of results across studies supports the meta-analysis's overarching conclusions.

Potential Impact of SC-EVs on Pancreatitis

Extracellular vesicles are membranous structures released by various cell types, capable of delivering their cargo (including transcription factors, oncogenes, microRNAs, and mRNAs) to recipient cells by directly binding to their plasma membranes. They are also present in physiological

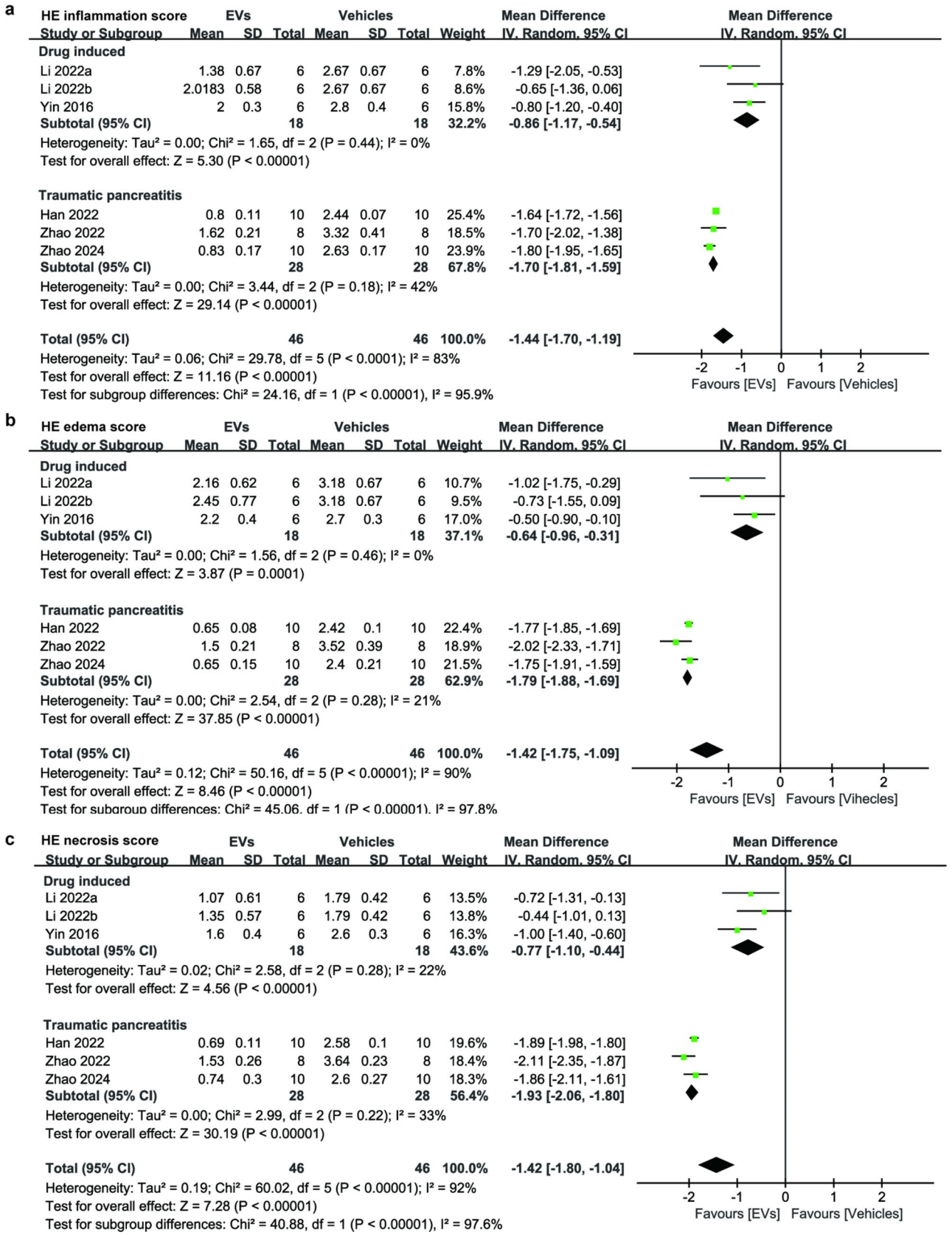

Fig. 4 Subgroup analysis of the effect of EVs treatment on the HE edema score of pancreas after SAP. (**a**) the inflammation score. (**b**) the edema score. (**c**) the necrosis score

fluids such as blood, urine, and amniotic fluid, playing roles in numerous physiological and pathological processes, including immune responses, coagulation, inflammation, and cancer progression, through intercellular communication [27–29]. The efficacy and mechanism of EVs from different cellular sources in pancreatitis remain unclear. Following pancreatitis induction by injuries, vesicular cells within the pancreas release factors that recruit immune cells and trigger inflammatory responses, exacerbating pancreatitis. Alveolar cell-derived EVs interact with macrophages via ITGAM and ITGB2, inducing pancreatic inflammatory cell infiltration and promoting pancreatitis progression and systemic injury [30]. Macrophage-derived EVs infiltrate pancreatic β-cells, fusing with and disrupting β-cell mitochondria, leading to lipid peroxidation and apoptosis [31]. Moreover, plasma EVs serve as a valuable diagnostic tool for SAP. Circulating exosome levels correlate with pancreatic inflammation severity [32, 33]. Plasma exosome expression is notably elevated in SAP rats, contributing to SAP-associated acute lung injury [34]. Furthermore, EVs isolated from the plasma of mild and severe pancreatitis patients exhibit distinct metabolic profiles, with distinct biomarkers predicting SAP with high accuracy [35].

Exogenously administered mesenchymal stem cells have demonstrated beneficial effects in treating SAP. Moreover, MSCs release a substantial quantity of EVs that exhibit comparable biological activity to MSCs, suggesting EVs as a promising whole-cell therapeutic alternative for pancreatitis treatment [36]. A recent study revealed that EVs effectively suppressed the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α, while simultaneously enhancing IL-10 secretion through counteracting PAMP-induced macrophage activation. Furthermore, the potent anti-inflammatory properties of EVs contribute to tissue repair and angiogenesis [37]. Moreover, inflammation contributes to pancreatic enzyme-induced tissue damage, leading to alveolar cell death and triggering localized, even systemic inflammatory responses. Treatment with hUC-MSCs-EVs notably attenuated TNFα-induced necrotic apoptosis of alveolar cells [23]. Acute lung injury is the most common and earliest complication associated with SAP. In the Na-T-induced SAP model, elevated levels of plasma exosomes reached the alveoli, resulting in the conversion of macrophages from the M2 to the M1 phenotype [30, 38]. Plasma exosomes derived from rats pretreated with rhodopsin exhibited significant attenuation of lung injury in SAP rats by suppressing inflammation, which was linked to altered miRNA expression [39]. Recent findings indicate that the secretory profile of MSCs is significantly influenced by exposure to different environments, with pretreated MSCs exhibiting enhanced performance in response to specific disease conditions [40–42]. Studies included in this meta-analysis revealed that TNF-α-pretreated EVs exhibited enhanced inhibition of pancreatic inflammatory response and pro-inflammatory factor release, while hypoxia-pretreated EVs demonstrated greater suppression of inflammatory factor secretion, tissue myeloperoxidase expression, and serum amylase levels [19, 22, 23]. Traumatic pancreatitis, mainly resulting from abdominal trauma, poses a significant risk of mortality and lacks effective interventions. Pooled analysis of three studies demonstrated significant efficacy of EVs in alleviating post-traumatic pancreatic inflammation and inflammatory factor release [20, 25, 26]. However, research in this area remains in its early stage, requiring further experiments to elucidate the specific mechanisms and interventions of EVs in TP.

EVs, natural carriers of DNA, RNA, and proteins, are potential drug delivers. While EVs therapeutic efficacy significantly depends upon their half-life and effective concentration at the site of injury [43]. The present study included in this analysis observed a dose-dependent relationship between EVs and the inhibition of TNF-α secretion in the drug-induced SAP model. EVs injected at doses > 200 μg exhibited superior efficacy (SMD = −4.37, 95% CI: −5.79, −2.95, $Tau^2 = 0.00$, $I^2 = 0\%$) compared to the 200 μg group (SMD = −2.52, 95% CI: −4.13, −0.91, $Tau^2 = 0.58$, $I^2 = 41\%$) ($p = 0.001$). Recent investigations have sought to enhance the stability, circulating half-life, and targeting capability of EVs in vivo [44]. Initial studies indicated rapid accumulation and clearance of intravenously injected EVs in the liver, spleen, and lungs. To prolong EVs' circulating half-life and enhance efficacy, tissue-engineered packaging technologies such as nano-encapsulation, hydrogel encapsulation, and peptide coupling have been explored, enhancing EVs' targeting properties [45, 46]. Despite these advancements, the field of EVs preparation and optimization remains in the exploratory stage, bearing significant scientific and clinical relevance.

Limitations and Future Research

This study has several limitations. Firstly, the small number of included studies and their limited sample sizes may impact the stability and reliability of the results. Secondly, most studies grouped before intervention, and proper allocation concealment was lacking, potentially leading to an overestimation of the experimental effect. Significant heterogeneity was observed among the included studies, probably attributed to variations in methodological quality, small sample sizes, and differences in interventions, control group treatments, EVs dosages, and frequencies. The majority of evidence quality was rated as low, with insufficient data plots to support the findings adequately. Further high-quality, robust randomized controlled trials are warranted to

provide clearer insights into the therapeutic efficacy of EVs in severe acute pancreatitis.Thirdly, animal models failed to fully replicate clinical pathological processes. Acute pancreatitis can arise from multiple potential causes. Among the nine experiments included in this meta-analysis, six utilized the bile salt analog-induced acute pancreatitis model. This model partially simulates bile reflux caused by bile stone obstruction of the bile ducts, which can lead to pancreatitis and pancreatic damage. However, it is challenging to fully replicate the multifactorial effects of bile stones, such as mechanical injury and chemical stimulation. The trauma model, on the other hand, is more appropriate for mimicking traumatic acute pancreatitis, as it induces local inflammation and tissue damage in the pancreas through direct compression. Notably, our subgroup sensitivity analyses revealed that heterogeneity in pancreatic HE scores was significantly influenced by the SAP model. This heterogeneity was mitigated through subgroup analyses. It is important to acknowledge that both animal models have inherent limitations in fully elucidating the pathogenesis of pancreatitis or in evaluating therapies, largely due to individual variability and the complex systemic responses associated with the condition. Future efforts should focus on improving these models to better replicate the multifactorial characteristics of human pancreatitis.

Conclusion

Our study highlights the advantages of SC-EVs in treating severe acute pancreatitis, demonstrating substantial efficacy in mitigating inflammation and ameliorating pancreatic histopathological damage. However, the sourcing, extraction, and interventions related to EVs are still in the early stages of investigation. Further preclinical studies are imperative to ensure the safety and efficacy of EVs interventions for clinical application in SAP therapy.

Abbreviations

SC-EVs	Stem cell-derived extracellular vesicles
SAP	Severe acute pancreatitis
TP	Traumatic pancreatitis
IL-6	Interleukin 6
IL-10	Interleukin 10
TNF-α	Tumor necrosis factorα
MSCs	Mesenchymal stem cells
EVs	Extracellular vesicles
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SYRCLE	Systematic Review Center for Laboratory Animal Experiments
NTA	Nanoparticle Tracking Analysis

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12015-025-10852-5 .

Authors' Contribution Y. H, M.Y and J.W were responsible for experimental design, project conception, data extraction, writing, revising and editing the manuscript. Y.H and M.Y performed statistical analysis. J.W and L.H revised this manuscript. L.H provided funding support. All the authors read and approved the final version.

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Data Availability Study data were presented in the manuscript and supplemental materials. More information in current study are available from the corresponding author on reasonable request.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare that they have no competing interests.

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