Received: 10 May 2024 | Accepted: 22 August 2024

DOI: 10.1111/jebm.12635

ARTICLE

WILEY

Effects of integrated traditional Chinese and Western medicine for acute pancreatitis: A real-world study in a tertiary teaching hospital

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Funding information
Project of Sichuan Provincial Administration of Traditional Chinese Medicine Innovation Research Team, Grant/Award Number: 2023ZD04; Project of Sichuan Provincial Administration of Traditional Chinese Medicine, Grant/Award Number: 2020ZD004; National Natural Science Foundation of China, Grant/Award Numbers: 82074230, 82104715

Abstract

Aim: This study aimed to evaluate whether integrated traditional Chinese medicine (TCM) and Western medicine (WM) is more effective than WM for acute pancreatitis (AP).

Methods: Patients with AP were enrolled and divided into the TCM and WM (TCM&WM) and WM groups according to the therapeutic protocol in real clinical settings. We applied 1:3 propensity score matching, which was to adjust confounding factors. The primary outcome was mortality, whereas the secondary outcomes were organ failure, organ supportive therapies, local complications, hospitalization cost, and length of hospital stay. Sensitivity and subgroup analyses were also performed.

Results: Of 5442 patients with AP, 4691 and 751 were included in the TCM&WM and WM groups, respectively. After PSM, patient baseline characteristics were well balanced. Compared with the WM group (n = 734), the TCM&WM group (n = 2096) had lower overall mortality rate (1.7% vs. 3.4%; risk ratio, 0.482; 95% confidence interval, 0.286–0.810; p = 0.005). The TCM&WM group was associated with lower risk of persistent renal failure, multiple organ failure, and infection, lower utilization

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of organ supportive therapies, shortened lengths of hospital and intensive care unit stay, and lower hospital costs. Sensitivity analyses showed similar results. Subgroup analysis favored TCM&WM treatment for patients aged < 60 years, with hypertriglyceridic etiology, and with admission interval between 24 and 48 h.

Conclusion: TCM&WM treatment can achieve lower risks of mortality and organ failure and better economic effectiveness in patients with AP than WM treatment. This study provides a promising alternative of TCM&WM treatment for AP in the real-world setting.

KEYWORDS

acute pancreatitis, heat-disease theory, integrated traditional Chinese and Western medicine, real-world study, Western medicine

1 | INTRODUCTION

Acute pancreatitis (AP) is a digestive disorder common worldwide. The well-known causes of AP are gallstones, alcohol misuse, and hypertriglyceridemia, which trigger premature intracellular activation of pancreatic enzymes and lead to consequent pancreatic injury and systemic inflammation.[1] The incidence of AP is 34 per 100,000 individuals[2,3] and is increasing worldwide.[4] Although approximately 60% of patients with AP present with a mild form and achieve full recovery within a few days with supportive care, approximately 20–30% who develop a moderate or severe form with necrosis of the pancreatic or peripancreatic tissue, organ failure (OF), or both have an increased substantial mortality rate of 20–40%.[5,6] Severe acute pancreatitis (SAP), which is characterized by OF persisting for > 48 h, has an incidence rate of approximately 15–20% and a mortality rate of 36–50%.[7] As there remains no specific and effective pharmacological therapy for AP, the challenge of AP remains in managing severe cases and complications associated with the disease.

Traditional Chinese medicine (TCM) is increasingly used worldwide for the prevention and treatment of diseases. In TCM theory, AP is categorized into "abdominal pain," "spleen and heart pain," "stomach and heart pain," and "pancreatic disease." TCM has been widely used for the treatment of AP in China and showed promising therapeutic effects. Chinese medicinal compounds or monomers with rhubarb as a representative component can improve pancreatic microcirculation in animal models of SAP,[8] antagonize oxidative stress injury and inflammation,[9,10] and promote the recovery of intestinal function.[11] Clinicians at West China Hospital have been exploring the integration of TCM and WM (TCM&WM) for the treatment of AP since the 1970s. During the long-term clinical practice, we summarized the heat-disease theory to elucidate the pathogenesis that AP is triggered and exploded by the invasion of "heat-evil" to the organs and proposed the treatment principle of "clearing heat, removing toxin, and purgation" (abbreviated as Yihuoqingxia).[12] Previous studies suggested TCM&WM nonsurgical treatment decreased the mortality compared with surgical treatment.[13,14] Nevertheless, there is a lack of high-quality evidence on the effectiveness of TCM&WM treatment.

To provide the evidence for the integration of TCM, we conducted a real-world cohort study using conventional WM treatment as a control to evaluate the treatment effects of integrated TCM&WM comparing with WM treatment.

2 | MATERIALS AND METHODS

2.1 | Setting and data source

Data were obtained from prospectively collected database of consecutive patients with AP admitted to West China Hospital of Sichuan University in Chengdu.[15] This hospital is the leading medical center for AP, with an average of > 2500 AP cases annually (Figure S1). This study complied with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[16] A multidisciplinary research team comprising physicians, epidemiologists, statisticians, and informatics experts established the acute pancreatitis database. Patients with AP were registered on admission. Data were extracted from electronic medical records. Severity scores and outcome measures were assessed by research assistants to establish a database. Experienced physicians reviewed the patients' data. Data quality control followed a standardized operation procedure. The study was approved by the West China Hospital of Sichuan University Clinical Trials and Biomedical Ethics Committee (No. 2019[1184]) and was registered on Chinese Clinical Trial Registry (No. ChiCTR2000033579).

2.2 | Patients

Patients were enrolled from a prospectively collected AP database if they were (1) aged between 18 and 80 years, (2) admitted within 72 h of symptom onset, and (3) hospitalized at West China Hospital between September 1, 2013, and August 31, 2019. The exclusion criteria were as follows: (1) pregnant or lactating women, (2) patients with a history of any neoplastic disease, and (3) patients in advanced or terminal stages of any disease.

2.3 | Grouping and therapeutic protocol

According to their treatment strategies, the patients were divided into the TCM&WM (those who were admitted to the Department of Integrated TCM and WM) and WM (those who were admitted in other departments) groups. Both groups of patients with AP received guideline-directed treatments, including fluid resuscitation, analgesia, nutrition, prevention of infectious complications, and surgery.[17,18]

In real clinical setting, the Department of Integrated TCM and WM (current "Pancreatitis Center") took priority over other departments to admit patients with AP and provided TCM&WM treatment under the guidance of the heat-disease theory. The therapeutic strategies were as follows: (1) oral and enema administration of a TCM decoction. In the acute phase, the patients received either oral intake (or nasogastric infusion, 10–100 mL), enema (200 mL), or both of the Chinese medicinal herb formula Chai-qin-cheng-qi decoction (CQCQD), from twice daily to once every 2 h at the physician's discretion. CQCQD mainly consisted of herbs and mineral medicines, as described previously,[19] and CQCQD for enema was modified and is listed in Table S1. In the recovery and late stages, TCM decoctions were prescribed based on the syndrome differentiation. (2) The Liu-He-Dan ointment was externally applied on the abdomen once daily until the abdominal pain was relieved. The instructions for the Liu-He-Dan ointment are available in the Supplementary Materials. (3) Electrical acupuncture was applied once daily for 20 min. (4) Regarding acupoint injection, neostigmine or metoclopramide was injected into the Zusanli (ST36) acupoint once or twice daily at the treating physician's discretion, if there was abdominal compartment syndrome. (5) Chinese patent injections were as follows: Shengmai, Shenmai, lyophilized salvianolate, Xueshuantong (lyophilized), and *Erigeron breviscapus* injections. The instructions for the Chinese patent injections are shown in Table S2.

Patients in the WM group admitted to other departments mainly received routine therapies but did not use the comprehensive TCM protocol described above. Further information on the treatments is available in the Supplementary Materials.

2.4 | Outcome

The primary outcome was mortality rate. The secondary outcomes included the incidence and duration of OF (respiratory, cardiovascular, and renal), incidence of local complications, severity grading, incidence of infectious pancreatic necrosis, operative rate, hospitalization costs, and length of hospital stay.

2.5 | Statistical analyses

All eligible cases from the clinical database were selected for data analysis, and no sample size calculation was performed. To adjust for confounding bias in the baseline characteristics between the groups, we used propensity score matching (PSM)[20,21] with a 1:3 matching ratio and the nearest-neighbor strategy with a caliper of 0.02. PSM was calculated by logistic regression models and estimated with the following variables: age, sex, interval from symptom onset to admission, Charlson Comorbidity Index (CCI), updated CCI, American Society of Anesthesiologists (ASA) physical status classification, history of alcohol consumption and smoking, referral, previous AP episode, etiology, admission laboratory tests, and severity scores. The selection of the above covariates was mainly based on the *p*-value of the baseline data and the advice of clinical experts. A standardized mean difference (SMD) of < 0.2 between the groups was considered a good balance of the matched cohort. Four sensitivity analyses, including standardized mortality ratio weighting (SMRW), inverse-probability of treatment weighting (IPTW), bivariate logistic regression, 1:4 PSM ratio, were performed to increase the statistical power of PSM analysis and to verify the robustness of the results. We also performed a subgroup analysis to determine the differences among the subgroups.

Categorical variables are summarized using numbers and percentages, whereas continuous variables are described using medians with interquartile ranges (IQR) for skewed distributions. Two-tailed p-value < 0.05 indicated statistically significant differences. The risk ratios (RRs) and 95% confidence intervals (CIs) were calculated. Missing data were addressed by multiple imputation. Data processing and statistical analyses were performed using R version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Patient screening and enrollment

In total, 5727 patients from September 1, 2013, to August 31, 2019, were initially extracted from the AP database. Finally, 5442 patients were included in the analysis, consisting of 4691 patients in the TCM&WM group and 751 patients in the WM group. A flowchart of the study is shown in Figure 1.

3.2 | Baseline characteristics of patients in the full and matched cohorts

The baseline characteristics of the TCM&WM and WM groups were compared (Table 1). Definitions of the study variables are available in the Supplementary Materials. In the full cohort, there were significant differences in the distributions of demographic and baseline characteristics between the two groups. Hyperlipidemia and biliary stone formation were the first two etiologies, among which hyperlipidemia and biliary stone formation were the most common etiologies in the TCM&WM and WM groups, respectively. Before matching, patients in the TCM&WM group were younger and had a higher proportion of male, shorter intervals from onset to admission, fewer referrals,

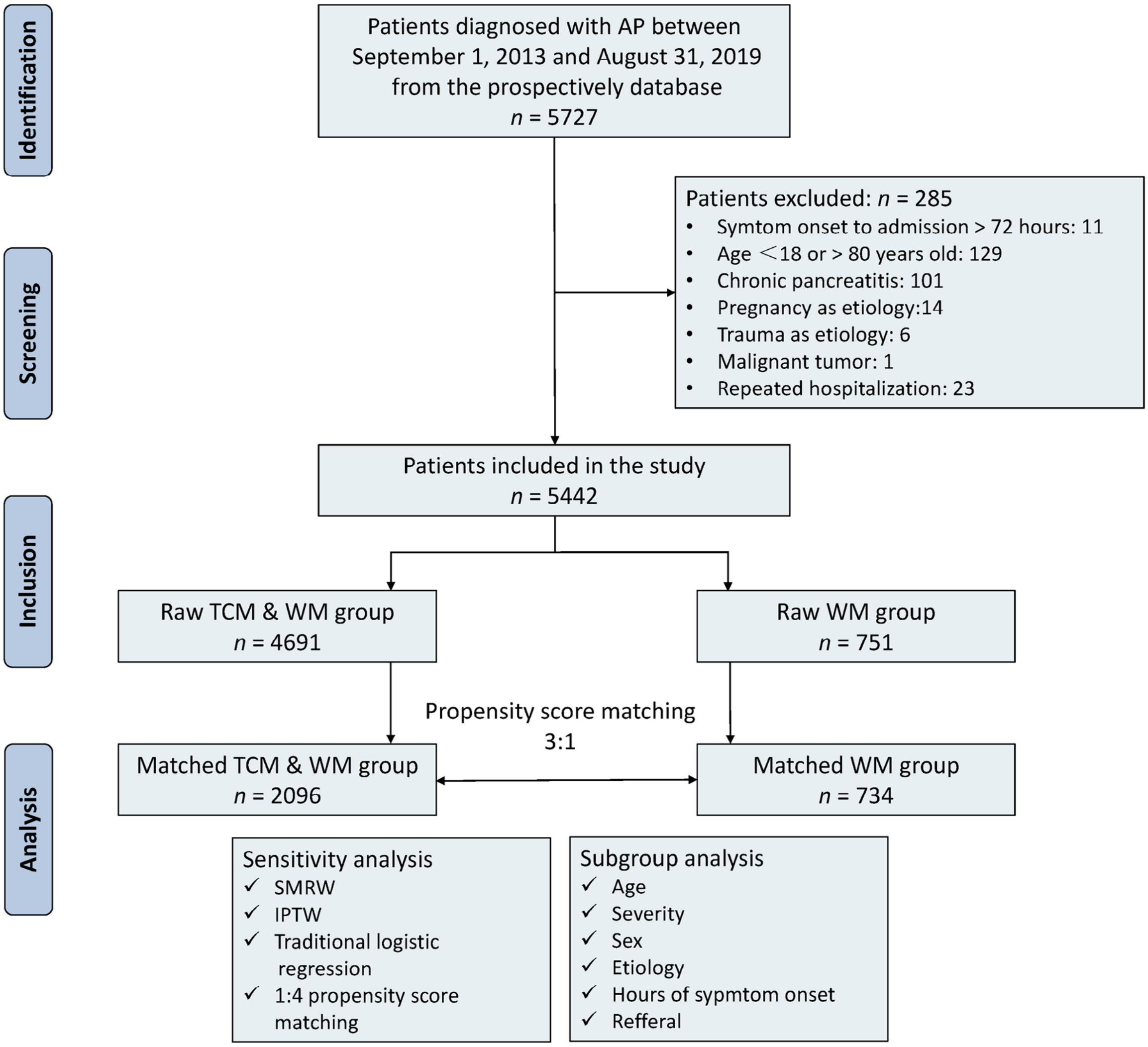

FIGURE 1 Flow chart of the study. AP, acute pancreatitis; IPTW, inverse-probability of treating weighting; SMRW, standardized mortality ratio weighting; TCM&WM, traditional Chinese and Western medicine; WM, Western medicine.

and lower severity clinical markers than those in the WM group. When setting a 3:1 matching ratio, 2096 patients were included in the TCM&WM group and 734 patients were included in the WM group. After matching, the characteristics were balanced between the TCM&WM and WM groups at baseline. The distribution of propensity scores in the TCM&WM and matched WM groups highly overlapped, indicating an acceptable quality of matching for our propensity score models (Figure S2). Among 2830 patients with AP in the PSM cohort, there were 1318 MAP (46.6%), 902 MSAP (31.9%), and 610 SAP (21.5%) (Figure 2).

3.3 | Effectiveness evaluation by propensity score matching analysis

The primary and secondary outcomes after matching are presented in Table 2. Treatment with TCM&WM was associated with a lower overall mortality rate of 1.7% versus 3.4% with WM treatment (RR, 0.482; 95% CI, 0.286–0.810; $p = 0.005$). Although there were no significant differences in the duration of persistent respiratory or circulatory failure between the two groups, the incidence rate and duration of renal failure were lower in the TCM&WM group than in the WM group. Compared with the WM group, the TCM&WM group had a significantly higher use of noninvasive positive pressure ventilation (NIPPV) (RR, 1.589; 95% CI, 1.234–2.046; $p < 0.001$) and lower use of invasive mechanical ventilation (IMV) (RR, 0.605; 95% CI, 0.437–0.838; $p = 0.034$), which was consistently observed for the duration of NIPPV ($p < 0.001$) and IMV support ($p = 0.002$). TCM&WM treatment had significantly lower use of continuous renal replacement therapy (CRRT) (RR, 0.426; 95% CI, 0.238–0.763; $p = 0.003$) and shorter duration of CRRT support ($p = 0.003$) than WM treatment. There was no statistically significant difference in the incidence of local complications between the two groups (all $p > 0.05$). The lengths of hospital stay and intensive care unit (ICU) stay were shorter in the TCM&WM group than in the WM group ($p = 0.017$), whereas the duration of high dependency unit stay was longer in the TCM&WM group than in the

TABLE 1 Baseline characteristics of patients with acute pancreatitis before and after propensity-score matching.

Parameters	Before matching TCM&WM (n = 4691)	Before matching WM (n = 751)	Before matching SMD	After matching TCM&WM (n = 2096)	After matching WM (n = 734)	After matching SMD
Age, years[a]	45 (38–52)	46 (38–56)	0.116	46 (38–55)	46 (38–55)	−0.001
Sex, male (%)	3086 (65.8)	457 (60.9)	0.101	1287 (61.4)	445 (60.6)	−0.016
Onset hours, hours[a]	24 (12–34)	24 (17–48)	0.323	24 (16–48)	24 (17–48)	−0.003
CCI[a]	0 (0–1)	0 (0–1)	0.029	0 (0–1)	0 (0–1)	−0.033
Updated CCI[a]	0 (0–0)	0 (0–0)	−0.074	0 (0–0)	0 (0–0)	−0.029
ASA classification (%)						
I	2241 (47.8)	356 (47.4)	−0.008	998 (47.6)	349 (47.5)	−0.002
II	2194 (46.8)	341 (45.4)	−0.028	960 (45.8)	334 (45.5)	−0.006
III	227 (4.8)	43 (5.7)	0.040	124 (5.9)	40 (5.4)	−0.022
IV	29 (0.6)	11 (1.5)	0.088	14 (0.7)	11 (1.5)	0.077
History of alcohol intake (%)	2049 (43.7)	325 (43.3)	−0.012	896 (42.7)	314 (42.8)	0.002
Referral (%)	2457 (52.4)	480 (63.9)	0.240	1316 (62.8)	465 (63.4)	0.012
Previous history of AP (%)	2259 (48.2)	232 (30.9)	0.373	668 (31.9)	232 (31.6)	−0.006
Etiology (%)						
Hypertriglyceridemia	1780 (37.9)	194 (25.8)	−0.262	624 (29.8)	193 (26.3)	−0.078
Biliary	986 (21.0)	231 (30.8)	0.225	497 (23.7)	228 (31.1)	0.167
Alcohol	187 (4.0)	45 (6.0)	0.092	100 (4.8)	42 (5.7)	0.040
Idiopathic	1061 (22.6)	127 (16.9)	−0.144	508 (24.2)	125 (17.0)	−0.179
Others	490 (10.4)	108 (14.4)	0.122	264 (12.6)	101 (13.8)	0.035
Mixed	187 (4.0)	46 (6.1)	0.096	103 (4.9)	45 (6.1)	0.053
Laboratory markers[a]						
Hematocrit, L/L	0.43 (0.39–0.46)	0.42 (0.38–0.46)	−0.133	0.42 (0.38–0.46)	0.42 (0.38–0.46)	0.008
Missing data (%)	24 (0.5)	13 (0.2)		–	–	
White blood cell counts, ×10^9/L	13.12 (9.97–15.85)	12.97 (9.88–16.77)	0.071	13.11 (9.91–16.43)	13.02 (9.97–16.76)	−0.008
Missing data (%)	21 (0.5)	13 (0.2)		–	–	
Albumin, g/L	41.30 (37.90–45.20)	40.40 (35.00–44.44)	−0.235	40.20 (36.20–44.30)	40.60 (35.38–44.50)	0.006
Missing data (%)	27 (0.6)	15 (0.2)		–	–	
Serum glucose, mmol/L	8.48 (6.35–11.46)	8.79 (6.57–12.10)	0.091	8.63 (6.37–11.91)	8.77 (6.54–11.94)	−0.006
Missing data (%)	26 (0.6)	19 (0.3)		–	–	
Blood urinary nitrogen, mmol/L	4.97 (3.68–6.20)	5.24 (3.80–6.90)	0.149	4.98 (3.69–6.50)	5.20 (3.78–6.80)	−0.023
Missing data (%)	29 (0.6)	18 (0.2)		–	–	
Creatinine, mmol/L	73 (60–84)	73 (59–90)	0.116	73 (59–86)	73 (59–90)	−0.001
Missing data (%)	28 (0.6)	16 (0.2)		–	–	
Triglycerides, mmol/L	5.09 (1.43–12.25)	2.91 (1.08–10.20)	−0.158	3.15 (1.14–9.77)	2.94 (1.07–10.62)	−0.001
Missing data (%)	55 (1.2)	34 (0.5)		–	–	
Lactate dehydrogenase, IU/L	247 (176–353)	258 (187–412)	0.147	252 (179–391)	256 (186–405)	−0.000
Missing data (%)	58 (1.2)	44 (0.6)		–	–	
Calcium ions, mmol/L	2.17 (1.97–2.31)	2.16 (1.97–2.30)	−0.098	2.16 (1.96–2.29)	2.17 (1.99–2.30)	0.067
Missing data (%)	52 (1.1)	33 (0.4)		–	–	

(Continues)

TABLE 1 (Continued)

Parameters	Before matching TCM&WM ($n = 4691$)	WM ($n = 751$)	SMD	After matching TCM&WM ($n = 2096$)	WM ($n = 734$)	SMD
Clinical severity scores[a]						
SOFA	0 (0–1)	0 (0–1)	0.095	0 (0–1)	0 (0–1)	−0.023
BISAP	1 (1–1)	1 (1–2)	0.174	1 (0–2)	1 (0–2)	−0.035
SIRS	2 (1–3)	2 (1–3)	−0.086	2 (1–3)	2 (1–3)	−0.022
GCS	1 (0–2)	1 (1–2)	0.242	1 (1–2)	1 (1–2)	−0.043
MCTSI	4 (2–6)	4 (2–6)	0.075	4 (2–6)	4 (2–6)	−0.008

Note: Values in parentheses are percentages unless indicated otherwise.
Abbreviations: AP, acute pancreatitis; ASA, American Society of Anesthesiologists; BISAP, bedside severity index score for acute pancreatitis; CCI, Charlson Comorbidity Index; GCS, modified Glasgow score; MCTSI, modified computed tomography severity index score; MMS, modified Marshall score; SIRS, systemic inflammatory response syndrome; SMD, standardized mean difference; TCM&WM, traditional Chinese and Western medicine; WM, Western medicine.
[a]Values are median (IQR).

WM group ($p < 0.001$). Furthermore, the TCM&WM group had significantly lower hospital costs than the WM group (¥16,556/person vs. ¥21,043/person, $p < 0.001$). Concomitant medications after matching are shown in Table 3. The use of cephalosporins was higher in the TCM&WM group than in the WM group, but the antibiotics of carbapenems, antifungals, β-lactams and their inhibitors, and glycopeptides were significantly lower than in the WM group ($p < 0.001$).

3.4 | Sensitivity and subgroup analyses

The findings of four sensitivity analyses (Tables 4 and 5) were generally consistent with those of the primary analysis. Subgroup analyses revealed a positive correlation between TCM&WM treatment and mortality. In the subgroup analyses for mortality stratified based on age, sex, etiology, severity, intervals from onset to admission, and referral, TCM&WM was associated with a lower risk of mortality among patients of aged < 60 years (1.37% vs. 3.54%; P = 0.001), SAP (6.56% vs. 13.72%; P = 0.006), male (1.48% vs. 3.15%; P = 0.026), with etiology of hypertriglyceridemia (1.76% vs. 7.25%; P < 0.001), and with admission intervals between 24 and 48 h (1.82% vs. 5.62%; P = 0.001), and referrals (2.50% vs. 4.95%; P = 0.010) compared with WM (Figure 3).

4 | DISCUSSIONS

This large-sample real-world cohort study involving patients with AP in a single tertiary healthcare setting showed that holistic treatment incorporating usual therapies with the administration of Chinese herbal decoctions and ointment, electric acupuncture, and acupoint injection resulted in an improved outcome. Compared with WM, TCM&WM was associated with lower mortality in AP and SAP. Moreover, analyses of the secondary outcomes showed that TCM&WM treatment was related to less OF and organ-supportive treatments, shorter hospitalization and ICU stay, and lower hospital costs than WM treatment. These findings are consistent with a range of sensitivity analyses of the primary and secondary outcomes.

To the best of our knowledge, this is the first real-world cohort study to show a positive outcome of the holistic treatment strategy of TCM&WM in AP. TCM is often used in combination with WM as an additional treatment. This complicated combination therapy has been applied to AP in a real-world setting. Studies on TCM for AP have been complicated by uncertainty over the optimal timing and duration of intervention modules and in the assessment of outcomes and controlling for confounding from comorbid conditions that are evident at the time of enrolment or arise as complications of the intervention. Previously, few clinical studies on the TCM treatment of AP have used a single intervention, for example, decoction or acupuncture. These trials have produced mixed results for intermediate outcome indicators because of the variability in the approaches used in clinical practice and the use of small sample sizes. These complexities represent the realities of clinical practice in AP and require sophisticated methods to reliably reveal the effects of TCM interventions.

To achieve this purpose, PSM, which is superior in improving the balance between two groups through a series of known covariates and poses a research paradigm in TCM, has been conducted in this study.[22] Other statistical approaches in the sensitivity analyses were applied to further control for confounding variables and minimize indication bias, which is a common and major threat to the validity of the findings. We set a caliper value of 0.02, which could eliminate 99% of the bias of unbalanced factors between the groups.[23] Although a 1:1 matching ratio usually provides more accurate and reliable results by ensuring comparability between the two groups, incomplete matching was achieved in this cohort using this ratio. We set a 1:3 PSM ratio to enlarge the matching samples, reduce sampling variance, and improve estimation accuracy. Furthermore, we performed weighted matching to test the accuracy and bias. Consequently, the consistency in findings

TABLE 2 Primary and secondary outcomes after matching.

Parameters	TCM&WM (*n* = 2096)	WM (*n* = 734)	Risk ratio (95% CI)	*p* Value
Primary outcome				
Mortality (%)	35 (1.7)	25 (3.4)	0.482 (0.286–0.810)	**0.005**
Secondary outcomes				
Persistent organ failure (%)				
Respiratory	438 (20.9)	148 (20.2)	1.046 (0.849–1.289)	0.673
Circulatory	65 (3.1)	33 (4.5)	0.680 (0.443–1.043)	0.075
Renal	64 (3.1)	35 (4.8)	0.629 (0.413–0.958)	**0.030**
Duration of organ failure, days[a]				
Respiratory	0 (0–1)	0 (0–1)	–	0.619
Circulatory	0 (0–0)	0 (0–0)	–	0.106
Renal	0 (0–0)	0 (0–0)↑	–	**0.037**
Multiple organ failure (%)	86 (4.1)	43 (5.9)	0.668 (0.472–1.002)	**0.050**
Organ support (%)				
NIPPV	361 (17.2)	85 (11.6)	1.589 (1.234–2.046)	**<0.001**
IMV	109 (5.2)	61 (8.3)	0.605 (0.437–0.838)	**0.002**
Inotropic agents	76 (3.6)	38 (5.2)	0.689 (0.462–1.027)	0.066
CRRT	26 (1.2)	21 (2.9)	0.426 (0.238–0.763)	**0.003**
Duration of organ support, days[a]				
NIPPV	0 (0–0)↑	0 (0–0)	–	**<0.001**
IMV	0 (0–0)	0 (0–0)↑	–	**0.002**
Inotropic agents	0 (0–0)	0 (0–0)	–	0.064
CRRT	0 (0–0)	0 (0–0)↑	–	**0.003**
Local complications (%)				
Acute peripancreatic fluid	901 (43.0)	311 (42.4)	1.026 (0.865–1.216)	0.772
Pancreatic/peripancreatic necrosis	217 (10.4)	75 (10.2)	1.015 (0.769–1.339)	0.918
Walled-off necrosis	6 (0.3)	4 (0.5)	0.524 (0.147–1.862)	0.512
Infected necrosis	31 (1.5)	11 (1.5)	0.987 (0.493–1.973)	1.000
Infection (%)				
Lung	199 (9.5)	113 (15.4)	0.576 (0.450–0.739)	**<0.001**
Blood	109 (5.2)	41 (5.6)	0.927 (0.641–1.341)	0.688
Urinary	20 (1.0)	8 (1.1)	0.874 (0.383–1.994)	0.749
Abdominal	23 (1.1)	25 (3.4)	0.315 (0.177–0.558)	**<0.001**
Severity (%)				0.863
Mild	973 (46.4)	345 (47.0)	0.977 (0.825–1.156)	
Moderately severe	666 (31.8)	236 (32.2)	0.983 (0.821–1.177)	
Severe	457 (21.8)	153 (20.8)	1.059 (0.862–1.301)	
Surgery (%)				
Necrosectomy	75 (3.6)	27 (3.7)	0.972 (0.621–1.521)	0.900
Cholecystectomy	108 (5.2)	38 (5.2)	0.995 (0.681–1.454)	0.979
Length of stay, days[a]	10 (7–15)	10 (8–15)	–	**0.035**
ICU admission (%)	76 (3.6)	25 (3.4)	1.067 (0.674–1.690)	0.782
ICU duration, days[a]	0 (0–0)	0 (0–0)↑	–	**0.002**
HDU duration, days[a]	0 (0–0)↑	0 (0–0)	–	**<0.001**
Hospital costs, ¥RMB[a]	15665 (9704–28547)	21025 (12187–34179)	–	**<0.001**

Note: Values in parentheses are percentages unless indicated otherwise. Bold value are of significant difference.
Abbreviations: CI, confidence intervals; CRRT, continuous renal replacement therapy; HDU, high dependency unit; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIPPV, noninvasive positive pressure ventilation; TCM&WM, traditional Chinese and Western medicine; WM, Western medicine.
[a]Values are median (IQR).

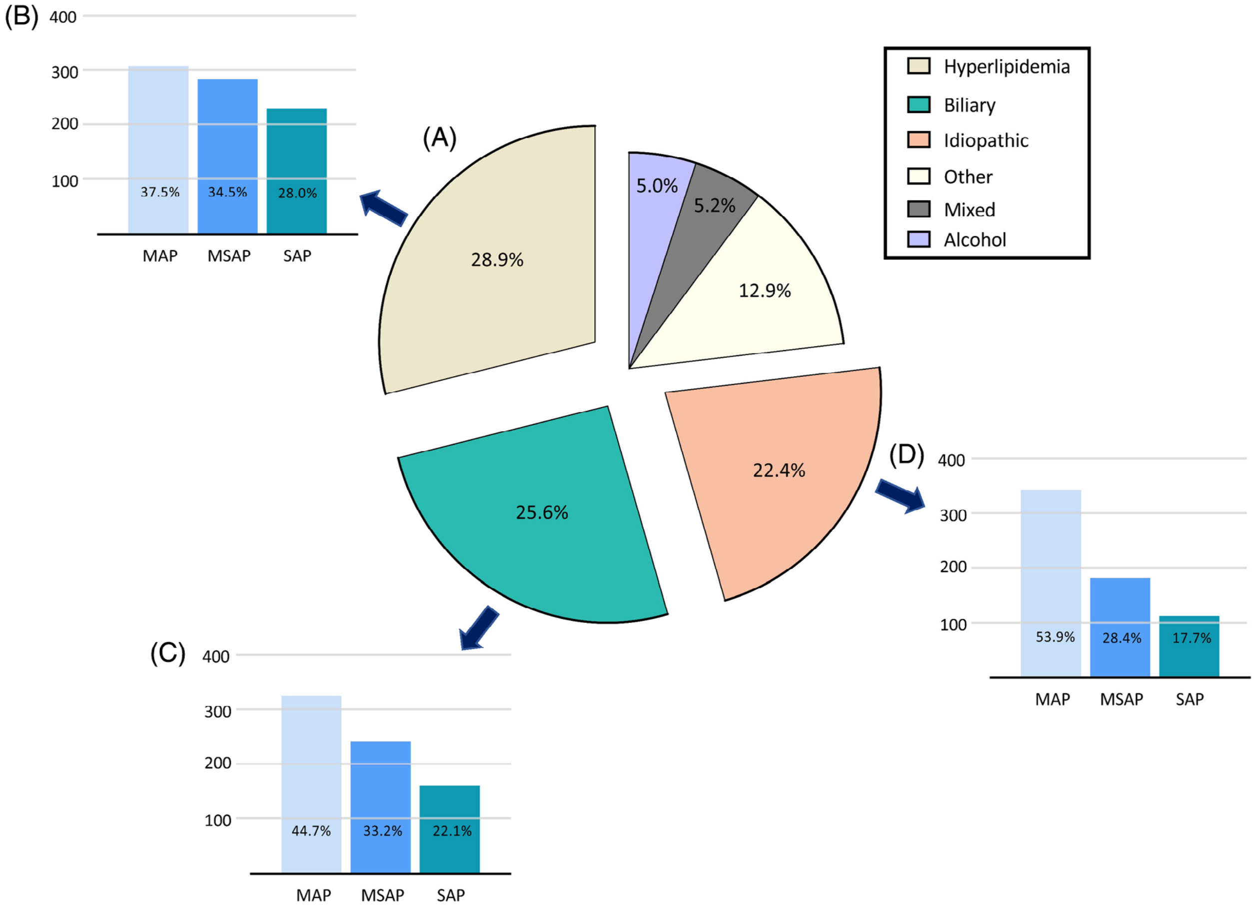

FIGURE 2 Etiologies (A) and severity proportions in (B) hyperlipidemic, (C) biliary, and (D) idiopathic acute pancreatitis after propensity score matching. MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis.

TABLE 3 Concomitant medications after matching.

Parameters	TCM&WM ($n = 2096$)	WM ($n = 734$)	Risk ratio (95% CI)	p Value
Medications (%)				
Somatostatin	806 (38.5)	615 (83.8)	0.121 (0.097–0.150)	**<0.001**
Ulinastatin	338 (16.1)	128 (17.4)	0.910 (0.728–1.138)	0.409
Octreotide	339 (16.2)	346 (47.1)	0.216 (0.180–0.261)	**<0.001**
Gabexate	466 (22.2)	427 (58.2)	0.206 (0.172–0.246)	**<0.001**
Proton pump inhibitors	2050 (97.8)	691 (94.1)	2.773 (1.814–4.240)	**<0.001**
Antibiotics (%)				
Carbapenems	197 (9.4)	175 (23.8)	0.331 (0.265–0.415)	**<0.001**
Cephalosporins	345 (16.5)	92 (12.5)	1.375 (1.074–1.760)	**0.011**
Quinolones	434 (20.7)	168 (22.9)	0.880 (0.719–1.077)	0.214
Antifungal	78 (3.7)	121 (16.5)	0.196 (0.145–0.264)	**<0.001**
Beta-lactams and beta-lactamase inhibitors	367 (17.5)	320 (43.6)	0.275 (0.228–0.330)	**<0.001**
Glycopeptides	46 (2.2)	24 (3.3)	0.664 (0.402–1.095)	0.107

Note: Bold value are of significant difference.
Abbreviations: CI, confidence intervals; TCM&WM, traditional Chinese and Western medicine; WM, Western medicine.

TABLE 4 Sensitivity analyses for primary outcome.

Sensitivity analysis	Primary outcome	Risk ratio (95% CI)	*p* Value
1:4 PSM ratio	Mortality	0.465 (0.284–0.761)	**0.002**
SMRW		0.653 (0.432–0.987)	**0.042**
IPTW		0.589 (0.362–0.959)	**0.031**
Traditional logistic regression		0.588 (0.343–1.007)	0.053

Note: Bold value are of significant difference.

Abbreviations: CI, confidence intervals; IPTW, inverse-probability of treating weighting; PSM, propensity-score matching; SMRW, standardized mortality ratio weighting.

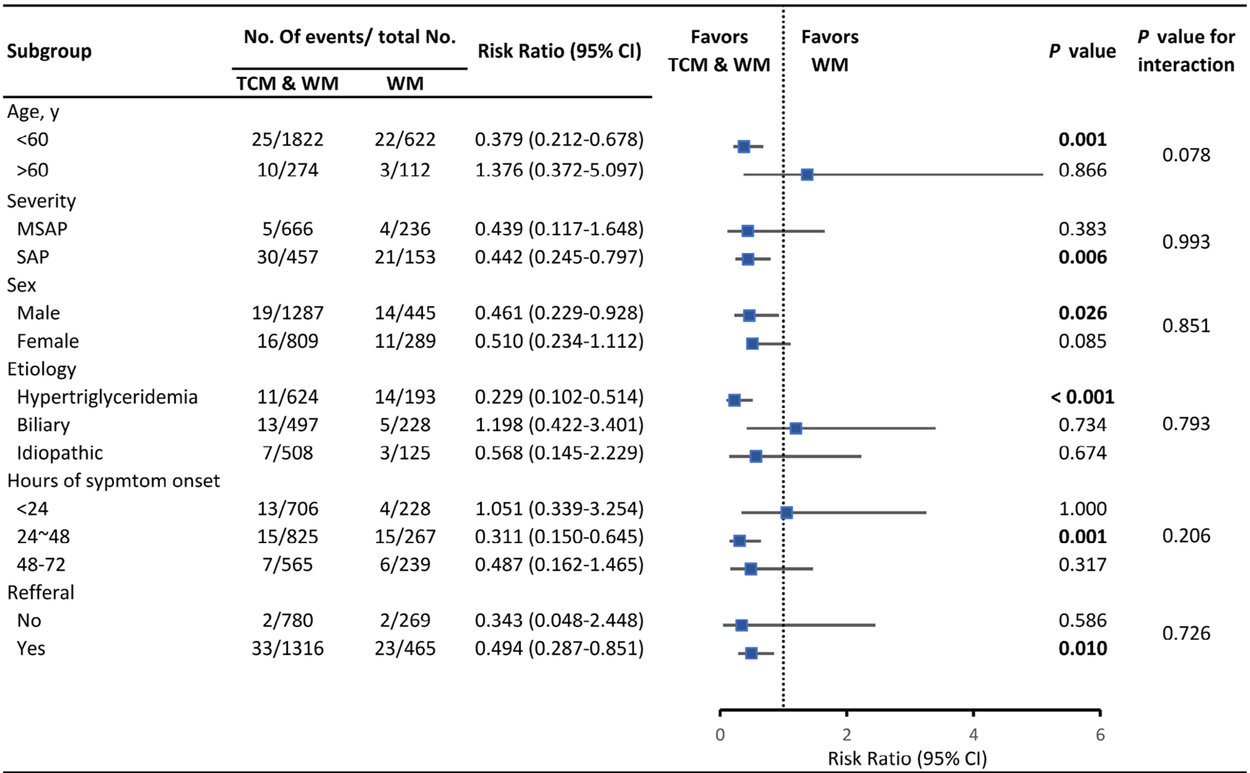

FIGURE 3 Subgroup analysis for mortality. CI, confidence intervals; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitisTCM&WM, traditional Chinese and Western medicine; WM, Western medicine.

using different methods has strengthened the strength of inference about the effect of TCM&WM.

The overall mortality of AP was 1.7% in the TCM&WM group and 3.4% in the WM group, which is lower than the current report of 2%.[1] Furthermore, the TCM&WM group had lower mortality rate of SAP than the WM group. The mortality rate of SAP in this cohort was significantly lower than the internationally reported mortality rate of 20%–40% and the domestic data reported by other affiliations.[24–26] Several potential reasons for the variability in mortality include differences in etiologies, intervals from disease onset to admission, referral patients, severity proportion, and treatment strategies.

In our hospital, patients with AP are preferentially admitted to the Department of Integrated TCM&WM from the emergency department by using the express admission process. Therefore, the number of patients in the TCM&WM group was approximately six times that of the WM group. Owing to the rich treatment experience and good follow-up education provided by the Department of integrated TCM&WM, patients with recurrent attacks preferred to visit our hospital directly and were admitted to our department. This mode can explain the shorter admission intervals, higher proportion of recurrent AP, and higher referral rate in the TCM&WM group than in the WM group. There were differences in conventional therapeutic strategies between the Department of Integrated TCM&WM and the other departments. The incidence of respiratory failure was comparable between the two groups; however, patients in the TCM&WM group were administered a higher proportion of NIPPV and had lower IMV usage than the patients in the WM group. This finding suggests that timely incorporation of NIPPV into TCM treatments can effectively

TABLE 5 Sensitivity analyses for secondary outcome.

Sensitivity analyses	Secondary outcome	Risk ratio (95% CI)	*p* Value
1:4 PSM	Multiple organ failure	0.651 (0.451–0.939)	0.021
	Persistent respiratory failure	1.010 (0.823–1.239)	0.927
	Persistent circulatory failure	0.657 (0.436–0.989)	0.043
	Persistent renal failure	0.590 (0.390–0.894)	0.012
	Duration of respiratory failure	–	0.678
	Duration of circulatory failure	–	0.064
	Duration of renal failure	–	0.008
	NPPV support	1.532 (1.190–1.971)	0.001
	IMV support	0.566 (0.431–0.775)	<0.001
	CRRT support	0.367 (0.207–0.650)	<0.001
	Duration of NPPV support	–	<0.001
	Duration of IMV support	–	<0.001
	Duration of CRRT support	–	<0.001
	Lengths of stay	–	0.068
	Hospital costs	–	<0.001
	ICU duration	–	<0.001
	HDU duration	–	<0.001
	Lung infection	0.626 (0.493–0.795)	<0.001
	Abdominal infection	0.318 (0.185–0.546)	<0.001
SMRW	Multiple organ failure	0.842 (0.616–1.150)	0.278
	Persistent respiratory failure	0.927 (0.768–1.119)	0.431
	Persistent circulatory failure	1.435 (0.996–2.067)	0.052
	Persistent renal failure	1.139 (0.812–1.597)	0.450
	Duration of respiratory failure	–	0.321
	Duration of circulatory failure	–	0.056
	Duration of renal failure	–	0.635
	NPPV support	1.623 (1.284–2.052)	<0.001
	IMV support	0.589 (0.446–0.776)	<0.001
	CRRT support	0.394 (0.249–0.625)	<0.001
	Duration of NPPV support	–	<0.001
	Duration of IMV support	–	<0.001
	Duration of CRRT support	–	<0.001
	Lengths of stay	–	0.022
	Hospital costs	–	<0.001
	ICU duration	–	<0.001
	HDU duration	–	<0.001
	Lung infection	0.719 (0.577–0.897)	0.003
	Abdominal infection	0.304 (0.191–0.482)	<0.001
IPTW	Multiple organ failure	0.761 (0.527–1.099)	0.144
	Persistent respiratory failure	1.080 (0.879–1.327)	0.462
	Persistent circulatory failure	0.758 (0.497–1.156)	0.197
	Persistent renal failure	0.701 (0.468–1.049)	0.082
	Duration of respiratory failure	–	0.405
	Duration of circulatory failure	–	0.211
	Duration of renal failure	–	0.217

(Continues)

TABLE 5 (Continued)

Sensitivity analyses	Secondary outcome	Risk ratio (95% CI)	*p* Value
	NPPV support	1.554 (1.206–2.002)	0.001
	IMV support	0.646 (0.468–0.890)	0.007
	CRRT support	0.414 (0.243–0.705)	0.001
	Duration of NPPV support	–	0.002
	Duration of IMV support	–	0.006
	Duration of CRRT support	–	0.004
	Lengths of stay		0.002
	Hospital costs	–	<0.001
	ICU duration	–	<0.001
	HDU duration	–	<0.001
	Lung infection	0.621 (0.491–0.785)	<0.001
	Abdominal infection	0.328 (0.196–0.547)	<0.001
Traditional logistic regression	Multiple organ failure	0.688 (0.439–1.078)	0.102
	Persistent respiratory failure	1.178 (0.909–1.528)	0.216
	Persistent circulatory failure	0.793 (0.503–1.248)	0.316
	Persistent renal failure	0.752 (0.467–1.211)	0.241
	NPPV support	2.393 (1.754–3.266)	<0.001
	IMV support	0.593 (0.421–0.835)	0.003
	CRRT support	0.440 (0.245–0.788)	0.006
	Lung infection	0.618 (0.481–0.793)	<0.001
	Abdominal infection	0.317 (0.185–0.541)	<0.001

Abbreviations: CI, confidence intervals; CRRT, continuous renal replacement therapy; HDU, high dependency unit; ICU, intensive care unit; IMV, invasive mechanical ventilation; IPTW, inverse-probability of treating weighting; NIPPV, noninvasive positive pressure ventilation; PSM, propensity-score matching; SMRW, standardized mortality ratio weighting.

improve oxygenation and alleviate respiratory failure, which can help attenuate the utilization of invasive ventilators.

The results of this study justify the scientific nature of the heat-disease theory in TCM, which has been proposed to summarize the pathogenesis and progression of AP. According to the heat-disease theory, qi blockage is the basic pathogenesis of AP, which corresponds to an inflammatory reaction. In the early stages of the disease, qi stagnates, depresses, combines with heat and dampness, and turns into fire, toxicity, and blood stasis. In the late stage of the disease, qi and blood disorders eventually lead to the decline of organs and the collapse of Yin and Yang. The diffusion of heat-evil and toxicity is the core mechanism arousing SAP to multiple OF and death. Therefore, TCM theories emphasize the prevention of organ injury by expelling heat-evil and purging the bowel. Previous studies have suggested TCM[27] and Chengqi series decoctions[28] were effective and safe for the treatment of AP in clinical practice. In real medical practice, patients with AP are admitted to the Department of Integrative TCM and WM and are administered Chinese herbal medicines, such as external compresses, acupuncture, acupoint injections, and ultrasound introduction of Chinese medicine. However, these Chinese medicinal options were not administered to patients with AP who were admitted to gastroenterology, ICU, surgery, or other related departments. They may be given rhubarb and mannitol by oral administration and enema; however, the TCM protocol was not directed under the heat-disease theory. A previous study with a small sample size indicated the effects of herbal decoctions administered via oral feeding and enema in reducing gastroenterological failure.[11] The incidence rate of acute necrotic collection was significantly lower in patients with SAP in the TCM&WM group than that in the WM group. We hypothesize that "activating blood circulation and removing blood stasis" in "Yihuo Qingxia" plays a role in reducing acute necrotic material accumulation. The incidence rate of pulmonary and abdominal infections in the TCM&WM group was significantly lower than that in the WM group, which is consistent with the results of our previous studies.

Our study has several strengths. First, we used a cohort with a large sample size and high-quality data to reliably assess the treatment effects of integrated TCM&WM in an integrative medicine setting. To the best of our knowledge, this is the first real-world study involving over 5000 patients with AP to investigate the effectiveness of integrated TCM and WM in the treatment of AP, guided by the TCM heat-disease theory. The findings fill a gap in the evaluation of the effectiveness of integrated TCM and WM in real-world practice. Second, there was no effective agent for us to apply active control in the study design, and we applied PSM to construct a counterfactual framework to ensure comparability between groups. We further performed sensitivity analyses to consolidate the results. We believe that the use of rigorous methods and the robustness of the findings through various sensitivity analyses substantially improved the strength of the findings.

There are a few limitations. Although we adjusted for a variety of confounders in the PSM, residual confounding from unmeasured factors could not be ruled out. Nevertheless, based on clinical experience, medical literature, and a large database, we included a large number of covariates for adjustment compared with similar studies. These factors cover a wide range of important domains that may affect the effect estimation, including demographic and clinical characteristics, comorbidities, complications, and concomitant medications. Owing to the nature of real-world studies characterized by a high degree of data heterogeneity, there remains a statistically significant difference in the distribution of the etiological factors, which may have some effects on outcome indicators. Residual confounding remains a challenging issue in real-world settings, and we hope that other studies will validate our results. Second, the data of this study were derived from the largest treatment center for AP in the West China Hospital, a major referral center and teaching hospital with > 2500 patients with AP annually. However, these findings may not be completely generalizable to all healthcare settings.

In conclusion, the results of this real-world study showed that holistic treatment with TCM&WM was superior to WM treatment in reducing the mortality rates of AP and SAP, attenuating the morbidity of OF and infection and their related invasive therapies, and providing higher economic health benefits.

ACKNOWLEDGMENTS

The authors thank all the staffs from multidisciplinary team for acute pancreatitis at West China Hospital of Sichuan University. The study was supported by funding from the Project of Sichuan Provincial Administration of Traditional Chinese Medicine Innovation Research Team (2023ZD04), the Project of Sichuan Provincial Administration of Traditional Chinese Medicine (2020ZD004), and the National Natural Science Foundation of China (82074230, 82104715).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Deng L, Chen Z, Zhu P, et al. Effects of integrated traditional Chinese and Western medicine for acute pancreatitis: A real-world study in a tertiary teaching hospital. *J Evid Based Med*. 2024;17:575–587. https://doi.org/10.1111/jebm.12635