Digestive and Liver Disease 56 (2024) 1023–1031

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

Peri-onset non-steroidal anti-inflammatory drugs use and organ failure in acute pancreatitis: A multicenter retrospective analysis

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ARTICLE INFO

Article history:
Received 17 July 2023
Accepted 19 December 2023
Available online 15 January 2024

Keywords:
Acute pancreatitis
Inverse probability of treatment-weighted analysis
Nonsteroidal anti-inflammatory drugs
Organ failure
Propensity score-matched analysis

ABSTRACT

Background: Organ failure (OF) of acute pancreatitis (AP) significantly contributes to AP-related mortality. Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with reduced complications of AP.
Aims: We aimed to investigate whether NSAIDs ameliorates SIRS and OF in patients with AP.
Methods: Eligible patients with AP were retrospectively identified in 4 hospitals between January 2015 and December 2018. Associations between peri-onset NSAIDs use (day -3 to day 3) and OF, persistent OF (POF), and SIRS within the first week were analyzed. Propensity score-matched (PSM) analysis and inverse probability of treatment-weighted (IPTW) analysis were used to estimate risk ratios.
Results: Among 1,528 patients with AP (97 [6.3%] with NSAIDs use), 242 (15.8%) developed organ failure, 89 (5.8%) progressed to POF, and 27 (1.8%) died within 3 months. PSM analysis showed no association between peri-onset NSAIDs and OF (risk ratio [RR], 1.00; 95% confidence interval [CI], 0.46 to 2.15) and POF (RR, 0.80; 95% CI, 0.21 to 2.98). IPTW analysis yielded similar results. Patients with and without peri-onset NSAIDs use were comparable with respect to OF, POF, and SIRS across subgroups defined by COX-2 selectivity and dose.
Conclusion: Peri-onset NSAIDs use was not significantly associated with reduced OF.

1. Introduction

Acute pancreatitis (AP) carries a mortality rate of 0.5 to 2.5%, and the incidence and associated healthcare costs are increasing [1,2]. Organ failure (OF), defined as failure of the respiratory, renal, or cardiovascular system [3], is the major determinant of severity and AP-related mortality [4,5]. Patients with persistent (>48 h) OF and transient (<48 h) OF are defined as severe and moderately severe AP and have a mortality rate of approximately 40% and 10%, respectively, whereas patients without OF have a mortality rate of only 2% [4]. Notably, 14.1% of AP patients develop OF despite the current standard of care [5], underscoring a pressing need for effective measures to reduce the risk and severity of AP-induced OF [3].

OF is mainly mediated by systemic inflammatory response attributed to AP-induced activation of the proinflammatory cytokine cascade. The activation of cyclooxygenase plays critical role in inciting the inflammatory cascade in AP through the formation of prostaglandin E_2 which has potent proinflammatory and vasodilating functions [6], implying that inhibition of cyclooxygenase might attenuate the inflammatory response and thereby reduce the risk and severity of OF in AP. Indeed, persistent SIRS (e.g., SIRS on day 4) after onset has been associated with AP-related mortality [7], and rectal nonsteroidal anti-inflammatory drugs (NSAIDs) administered in the periprocedural period effectively reduce the risk of pancreatitis after endoscopic retrograde cholangiopancreatography by 64% and almost eliminates the risk of severe pancreatitis [8,9].

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https://doi.org/10.1016/j.dld.2023.12.010
1590-8658/

Collectively, those studies suggested that peri-onset administration of NSAIDs might ameliorate the acute systemic inflammatory response and prevent OF.

The potential benefits and risks of NSAIDs in patients with AP are poorly understood. Although several retrospective studies reported an association between NSAIDs and reduced pancreatic necrosis, OF, and in-hospital mortality [2,10] in patients with AP, confounding resulted from the imbalance in baseline characteristics between patients with and without NSAIDs use (i.e., confounding by indication) was not accounted for in those studies. Given that NSAIDs may cause renal injury and gastrointestinal bleeding [11,12] and thus could instead induce or exacerbate OF in AP patients, the risk-benefit ratio of NSAIDs for AP patients of varying severity and chronic diseases remains unclear. Therefore, this study examined the real-world association between peri-onset NSAIDs use and OF, NSAIDs-associated adverse effects, and 3-month mortality in AP patients, controlling for confounding by indication and considering cyclooxygenase-2 (COX-2) selectivity and dose of NSAIDs.

2. Materials and methods

2.1. Study design, database, and case definition

This multicenter retrospective cohort study identified cases of AP from Integrative Medical Database, National Taiwan University Hospital (NTUH-iMD), an integrated hospital-based medical record database incorporating electronic medical records and administrative information from National Taiwan University Hospital (NTUH) and its branches located in northern and western Taiwan [13]. This comprehensive database has been prospectively maintained since its inception in 2013 and conforms to the Health Insurance Portability and Accountability Act (HIPAA). All individuals are de-identified. The study was approved by National Taiwan University Hospital Research Committee (202009074RIND). Given the electronic data were all de-identified in the academic hospital-based database, individual informed consent was not required according to Taiwan's Human Subject Research Act. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

Patients with a discharge diagnosis of AP (International Classification of Diseases [ICD 10]: K85.0, K85.1, K85.2, K85.3, K85.8, K85.9, B25.2; ICD 9: 577.0, 072.3) between January 2015 and December 2018 in a tertiary referral center (NTUH), two secondary referral centers (NTUH Hsing-Chu branch and NTUH Yun-Lin branch), and one primary hospital (NTUH Jing-Shan branch) were identified from the database. Only the first attack of AP was included for patients with recurrent AP attacks during the study period. The date on which features of AP on cross-sectional imaging or lipase level >3 times the upper limit of normal was identified, whichever occurred first, was designated as the index date (day 1). The inclusion and exclusion of AP patients are shown in supplementary Fig. S1.

2.2. Use of NSAIDs, aspirin, statins, and intravenous fluid

Patients who received oral or intravenous NSAIDs between 3 days preceding and 3 days after the index date (i.e., day −3 to day 3) with an overall cumulative dose exceeding 1 daily defined dose (DDD), defined as the recommended maximum daily dose for each NSAID generic, were adjudicated as peri-onset NSAIDs users. The NSAIDs included COX-2 non-selective NSAIDs (naproxen, acemetacin, indomethacin, diclofenac, intravenous ketorolac, and intravenous tenoxicam) and COX-2 selective NSAIDs (meloxicam, etoricoxib, and celecoxib). Information on NSAIDs use was extracted from prescription records (emergency department, inpatient, and outpatient), and medication administration records in emergency department and ward. We defined cumulative NSAIDs dose up to 0.5 DDD, 0.5 DDD to 1.5 DDD, and more than 1.5 DDD as low, medium, and high dose, respectively. Patients who received any dose of aspirin within 60 days prior to index date were adjudicated as aspirin users and those who received atorvastatin, rosuvastatin, and simvastatin were categorized as users of statin. Crystalloid fluid, including normal saline and Ringer's lactate solution, was calculated for total volume given within 48 h, with the proportion of Ringer's lactate specified.

2.3. Comorbidity, acute physiology and chronic health evaluation II scores, and laboratory data

The Charlson Comorbidity Index score was calculated based on the diagnosis codes in outpatient and inpatient electronic medical records before the index admission [14]. We extracted baseline characteristics (i.e., age, gender, smoking and alcohol status, body mass index), laboratory data (i.e., haematocrits, serum triglycerides, blood urea nitrogen, C-reactive protein), parameters of Acute Physiology and Chronic Health Evaluation II (APACHE II) scores on the index date from the electronic medical records [15].

2.4. Outcomes

The primary outcome was OF, a composite outcome comprising new-onset failure of any of the cardiovascular, renal, and respiratory systems which were previously healthy according to the revised Atlanta Classification [3] or worsening of pre-existing OF. In patients with multiple OF, the onset of the first failed organ was designated as the onset of OF.

The secondary outcomes were persistent OF, failure of the individual organ (i.e., cardiovascular, respiratory, renal), presence of SIRS (two or more of the four criteria consisting of temperature [>38 °C or <36 °C], heart rate >90 beats/minute, respiratory rate >20/minute or blood PCO2 < 32 mmHg, and leucocytosis/leukopenia [>12,000/mm^3 or <4000/mm^3]) [3] on day 1 and day 4, the presence of SIRS and daily SIRS scores (number of criteria fulfilled) in the first 7 days, the difference between the maximal SIRS score within 7 days and day 1 SIRS score (Δ [$SIRS_{MAX,7\ days}$ to $SIRS_{Day1}$]), mortality in 3 months, and clinically significant gastrointestinal bleeding, defined as the performance of esophagogastroduodenoscopy for gastrointestinal bleeding and blood transfusion within 30 days after the index date.

2.5. Statistical analysis

Continuous variables were summarised as mean/standard deviations and median/interquartile range (IQR) if they were normally and non-normally distributed, respectively, and compared between groups by Mann-Whitney U test. Categorical variables were expressed as counts and percentages and compared using Fisher's exact test.

In crude analysis and subgroup analysis, risk ratios and 95% intervals were calculated with log-binomial regression model. Propensity score matching and inverse probability of treatment weighting were used to adjust for imbalance in baseline factors (e.g., renal diseases) that might influence the probability of NSAIDs use. In propensity score-matched analysis, the probability of peri-onset NSAIDs use was calculated using variables that might be positively or negatively associated with peri-onset NSAIDs use, including age, Charlson Comorbidity Index, etiology of AP,

Table 1
Patient characteristics and clinical outcomes according to peri-onset NSAIDs treatments received.

	Demographics before Matching			Demographics of PS-matched groups		
	NSAIDs users (n = 97)	NSAIDs non-users (n = 1431)	P	NSAIDs users (n = 97)	NSAIDs non-users (n = 97)	P
Age (mean, SD)	52.2 (17.2)	58.7 (17.6)	0.001	51.2 (17.2)	52.8 (17.0)	0.81
Gender (Women)	36 (37.1)	617 (43.1)	0.25	36 (37.1)	39 (40.2)	0.66
BMI (mean, SD)	26.0 (4.0)	24.9 (4.4)	0.02	26.0 (4.0)	25.7 (4.9)	0.65
Smoking (n, %)	27 (27.3)	324 (35.1)	0.14	27 (27.8)	26 (26.8)	0.90
Alcohol drinking (n, %)	22 (24.3)	288 (24.3)	0.40	22 (22.7)	19 (9.8)	0.51
Aetiology of acute pancreatitis (n, %)			0.52			0.74
Biliary pancreatitis	29 (29.9)	453 (31.7)		29 (29.9)	30 (30.9)	
Alcoholic pancreatitis	14 (14.4)	242 (16.9)		14 (14.4)	15 (15.5)	
Hypertriglyceridemic pancreatitis	9 (9.3)	83 (5.8)		9 (9.3)	5 (5.2)	
Other causes	45 (46.4)	653 (45.6)		45 (46.4)	47 (48.5)	
Pre-existing comorbidity (n, %)						
Myocardial infarction	3 (3.1)	29 (2.0)	0.45	3 (3.1)	1 (1.0)	0.62
Congestive heart failure	3 (3.1)	82 (5.7)	0.27	3 (3.1)	4 (4.1)	1.00
Peripheral vascular disease	2 (2.1)	20(1.4)	0.65	2 (2.1)	1 (1.0)	1.00
Cerebrovascular disease	5 (5.2)	120 (8.4)	0.26	5 (5.2)	7 (7.2)	0.77
Dementia	6 (6.2)	44 (3.1)	0.10	6 (6.2)	1 (1.0)	0.05
Chronic pulmonary disease	6 (6.2)	99 (6.9)	0.78	6 (6.2)	3 (3.1)	0.31
Rheumatic disease	6 (6.2)	17 (1.2)	0.002	6 (6.2)	4 (4.1)	0.52
Peptic ulcer disease	3 (3.1)	120 (8.4)	0.06	3 (3.1)	3(3.1)	1.00
Liver disease, mild	11 (11.3)	126 (8.8)	0.40	11 (11.3)	14 (14.4)	0.67
Diabetes without chronic complications	15 (15.5)	230 (16.1)	0.87	15 (15.5)	17 (17.5)	0.70
Renal disease, mild to moderate	2 (2.1)	124 (8.7)	0.02	2 (2.1)	1 (1.0)	0.56
Diabetes with chronic complications	2 (2.1)	67 (4.7)	0.23	2 (2.1)	5 (5.2)	0.45
Liver disease, moderate to severe	0 (0)	21 (1.5)	0.64	0 (0)	2 (0)	0.50
Renal disease, severe	4 (4.1)	77 (5.4)	0.59	4 (4.1)	2 (2.1)	0.68
HIV infection, no AIDS	1 (1.0)	2 (0.1)	0.18	1 (1.0)	0 (0)	1.00
AIDS	2 (2.1)	27 (1.9)	0.71	2 (2.1)	2 (2.2)	1.00
'Scores and laboratory tests on admission						
Charlson Comorbidity Index (median, IQR)	0 (0–1)	0 (0–1)	0.86	0 (0–1)	0 (0–1)	0.53
APACHE II score (median, IQR)	7 (5–11)	9 (6–14)	0.003	7 (5–11)	7 (5–11)	0.49
SIRS score on day 1 (median, IQR)	1 (0–2)	1 (0–2)	0.29	1 (0–2)	1 (0–2)	0.84
Hematocrit (Hct,%, mean, SD)	40.7 (6.4)	39.9 (7.0)	0.29	40.7 (6.4)	41.5 (6.2)	0.38
Triglyceride (mg/dl, median, IQR)	176.5 (96–286)	121 (84–199)	0.02	176.5 (96–286)	125 (81–215)	0.11
BUN (mg/dl, median, IQR)	12.5 (9–21.1)	15.5 (10.1–26)	0.03	12.5 (9–21.1)	15.7 (9–22)	0.69
CRP (mg/dl, median, IQR)	2.5 (0.3–13.8)	2.5 (0.4–9.8)	0.94	2.5 (0.3–13.8)	2.8 (0.5–10.6)	0.86
Aspirin use in recent 60 days (n, %)	5 (5.2)	108 (7.6)	0.38	5 (5.2)	7 (7.2)	0.55
Statin use in recent 60 days (n, %)	6 (6.2)	92 (6.4)	0.93	6 (6.2)	10 (10.3)	0.30
Crystalloid volume within 48 h (mL, SD, NS and Lactate Ringer's)	1672.7 (1314.3)	1579.3 (1360.8)	0.51	1672.7 (1314.3)	1720.1 (1243)	0.80
Proportion of Ringer's Lactate in Crystalloid fluid (%)	0.06 (0.2)	0.09 (0.2)	0.36	0 (0)	0 (0)	0.19
NSAIDs use in each hospital (n, %)			0.005			0.93
Hospital 1 – tertiary center	30 (30.9)	543 (38.0)		30 (30.9)	26 (26.8)	
Hospital 2 – primary hospital	4 (4.1)	47 (3.3)		4 (4.1)	4 (4.1)	
Hospital 3 – secondary center	48 (49.5)	470 (32.8)		48 (49.5)	52 (53.6)	
Hospital 4 – secondary center	15 (15.5)	371 (25.9)		15 (15.5)	15 (15.5)	

APACHE II score, acute physiology and chronic health evaluation II score; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; HIV, human immunodeficiency virus; IQR, interquartile range; NSAIDs, non-steroidal anti-inflammatory drugs; PS, propensity score; SD, standard deviation.

Table 2
Peri-onset NSAIDs use and outcomes in patients with acute pancreatitis – crude analysis.

	NSAIDs users no. of events/total no. (%)	NSAIDs non-users	Risk ratios (95% CI)	*P*
Organ failure during admission				
Overall organ failure	12/97 (12.4)	230/1431 (16.1)	0.77 (0.45–1.32)	0.34
Cardiovascular failure	5/97 (5.2)	103/1431 (7.2)	0.72 (0.30–1.72)	0.45
Renal failure	6/97 (6.2)	86/1431 (6.0)	1.03 (0.46–2.29)	0.94
Respiratory failure	9/97 (9.3)	151/1431 (10.6)	0.88 (0.46–1.67)	0.69
Persistent organ failure	4/97 (4.1)	85/1431 (5.9)	0.69 (0.26–1.85)	0.47
ICU care during admission	5/97 (5.2)	168/1431 (11.7)	0.44 (0.18–1.04)	0.06
AP-related mortality in 3 months	1/97 (1.0)	26/1431 (1.8)	0.57 (0.08–4.14)	0.58
Clinically significant GI bleeding in 30 days	1/78 (1.3)	22/1013 (2.2)	0.59 (0.08–4.32)	0.60

AP, acute pancreatitis; ICU, intensive care unit; GI bleeding, gastrointestinal bleeding; NSAIDs, non-steroidal anti-inflammatory drugs.

receiving treatment sites, total volume of crystalloids within 48 h, proportion of Ringer's lactate solution in 48-hour crystalloid, and rheumatic, peptic ulcer, and renal diseases [16]. The matching algorithm first selected a patient with peri-onset NSAIDs use and then selected two patients without peri-onset NSAIDs use within a calliper width of 0.25 of the standard deviation of the logit of the propensity score. The data of paired groups were further analyzed to estimate the risk ratios (RRs) for outcomes. In inverse probability of treatment-weighted analysis, each patient was weighted by the inverse of the propensity score, whereas the RRs were calculated in doubly robust estimation [17,18]. To investigate the influences of NSAID type and dose, we estimated the average treatment effect for the treated (ATT), which approximated the risk difference between peri-onset NSAIDs users and non-users, in subgroups defined by COX-2 selectivity and NSAIDs dose with inverse probability of treatment weighting, using patients without peri-onset NSAIDs use as reference [16]. Because of the limited number of NSAIDs users in subgroups, propensity score-matched analyses were not conducted for subgroup analysis. To account for correlations between daily SIRS scores in each patient, we used generalized estimating equations to compare SIRS scores between NSAIDs users and non-users before and after propensity score matching. Missing information on vital signs (e.g., patients with admissions less than 7 days) were considered as within normal range in determining the presence or absence of SIRS or organ failure. Eight sensitivity analyses were conducted: changing the definition of peri-onset to between day −7 and day 7, to between day −3 to day −1, to between day −7 and day 1, to between day −7 and day 2, broadening the criteria of NSAIDs use to those with prior 60-day aspirin use or with NSAIDs use between day −3 and 3, excluding patients who were not admitted to ward, excluding patients who were lost to follow-up, and excluding those with unclear etiology of acute pancreatitis. SAS 9.4 (SAS Institute Inc., Cary, North Carolina) was used for propensity score-matched analysis and ATT estimation, and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) package "AIPW" for inverse probability of treatment-weighted analysis [17,18].

3. Results

3.1. Clinical characteristics

Among the 1528 patients with a confirmed diagnosis of AP between January 1, 2015 and December 31, 2018 (Figure S1), 97 (6.3%) patients had peri-onset NSAIDs use, 21 (21.6%) of whom received COX-2 selective NSAIDs. Compared with non-users, the peri-onset NSAIDs users were younger, had higher body mass index but lower APACHE II score on the index date and were less likely to have renal disease and peptic ulcer disease (Table 1).

3.2. Association between peri-onset NSAIDs use and clinical outcomes

Among the 1528 patients with AP, 242 (15.8%) patients developed OF, 173 (11.3%) patients required ICU admission, 89 (5.8%) patients had persistent OF, and 9 (0.6%) patients died of AP within 7 days after the index date. The median (IQR) of length of hospital stay was 6 days (2–10 days), whereas the average overall length of stay including emergency department and ward admissions was 9.3 days. Among patients with OF and persistent OF, 14 of 242 (5.8%) and 4 of 89 (6.5%) had exacerbation of pre-existing OF, respectively. Within 3 months after the index date, 27 (1.8%) patients died of AP. No significant differences were observed between patients with and without peri-onset NSAIDs with regard to the risk of either the primary or secondary outcomes (Table 2).

Among the 97 peri-onset NSAIDs users, 97 could be matched (1:1) to patients without NSAIDs use according to the propensity score. In the propensity score-matched analysis, NSAIDs users and non-users were comparable in the risk of OF (12.4% vs. 12.4%; risk ratio [RR], 1.00; 95% CI, 0.46 to 2.15). There were also no significant differences between the two groups with respect to the risk of persistent OF, cardiovascular, renal, and respiratory failure, as well as clinically significant gastrointestinal bleeding within 30 days (Table 3). The results of inverse probability of treatment-weighted analysis were in line with those of propensity score-matched analysis (Table 3). In subgroup analysis, the association between NSAIDs use and OF was not significantly different across predefined subgroups according to age, gender, Charlson Comorbidity Index scores, day 1 APACHE II score, and etiologies of pancreatitis (Fig. 1).

For sensitivity analysis, redefining peri-onset NSAIDs use as NSAIDs exposure between 7 days prior to (any dose) and/or 7 days after (more than 1 DDD) the index date, as NSAIDs exposure 3 days prior to the index date, or as any aspirin use in prior 60 days and/or NSAIDs between 3 days prior to (any dose) and/or 3 days after (more than 1 DDD) the index date showed no significant association between NSAIDs use and all outcomes (supplementary Table S1). Defining peri-onset NSAIDs use as any dose within 7 days before onset and/or more than 0.5 DDD within the first one or two days after onset also yielded similar results (supplementary Table S1). Secondly, excluding patients who were only treated at emergency department without ward admission, excluding those with unclear etiology of acute pancreatitis, or excluding those lost to follow-up after discharge also yielded similar results (supplementary Table S2).

3.3. Influences of COX-2 selectivity, and dose of NSAIDs

With inverse probability of treatment-weighted analysis, the risk of OF was 16.1% in patients without peri-onset NSAIDs use,

Table 3
Peri-onset NSAIDs use and outcomes in patients with acute pancreatitis.

	NSAIDs users no. of events/total no. (%)	NSAIDs non-users	Risk ratio (95% CI)	*P*
Propensity score-matched analysis				
Organ failure				
Overall organ failure	12/97 (12.4)	12/97 (12.4)	1.00 (0.46–2.15)	1.00
Cardiovascular failure	5/97 (5.2)	6/97 (6.2)	0.83 (0.25–2.73)	0.76
Renal failure	6/97 (6.2)	4/97 (4.1)	1.50 (0.42–5.32)	0.53
Respiratory failure	9/97 (9.3)	9/97 (9.3)	1.00 (0.40–2.52)	1.00
Persistent organ failure	4/97 (4.1)	7/97 (5.2)	0.80 (0.21–2.98)	0.74
AP-related mortality in 3 months	0/97 (0)	0/97 (0)	–	
Clinically significant GI bleeding in 30 days	1/78 (1.3)	2/78 (2.6)	0.50 (0.05–5.51)	0.57
Inverse probability treatment-weighted analysis				
Organ failure				
Overall organ failure	12/97 (12.4)	230/1431 (16.1)	0.77 (0.45–1.34)	0.82
Cardiovascular failure	5/97 (5.2)	103/1431 (7.2)	0.70 (0.29–1.71)	0.85
Renal failure	6/97 (6.2)	86/1431 (6.0)	1.05 (0.47–2.36)	1.02
Respiratory failure	9/97 (9.3)	151/1431 (10.6)	0.88 (0.46–1.68)	0.93
Persistent organ failure	4/97 (4.1)	85/1431 (5.9)	0.69 (0.26–1.88)	0.86
AP-related mortality in 3 months	1/97 (1.0)	26/1431 (1.8)	0.55 (0.07–4.32)	0.89
Clinically significant GI bleeding in 30 days	1/78 (1.2)	22/1013 (2.2)	0.56 (0.07–4.46)	0.90

AP, acute pancreatitis; NSAIDs, non-steroidal anti-inflammatory drugs; GI bleeding, gastrointestinal bleeding.

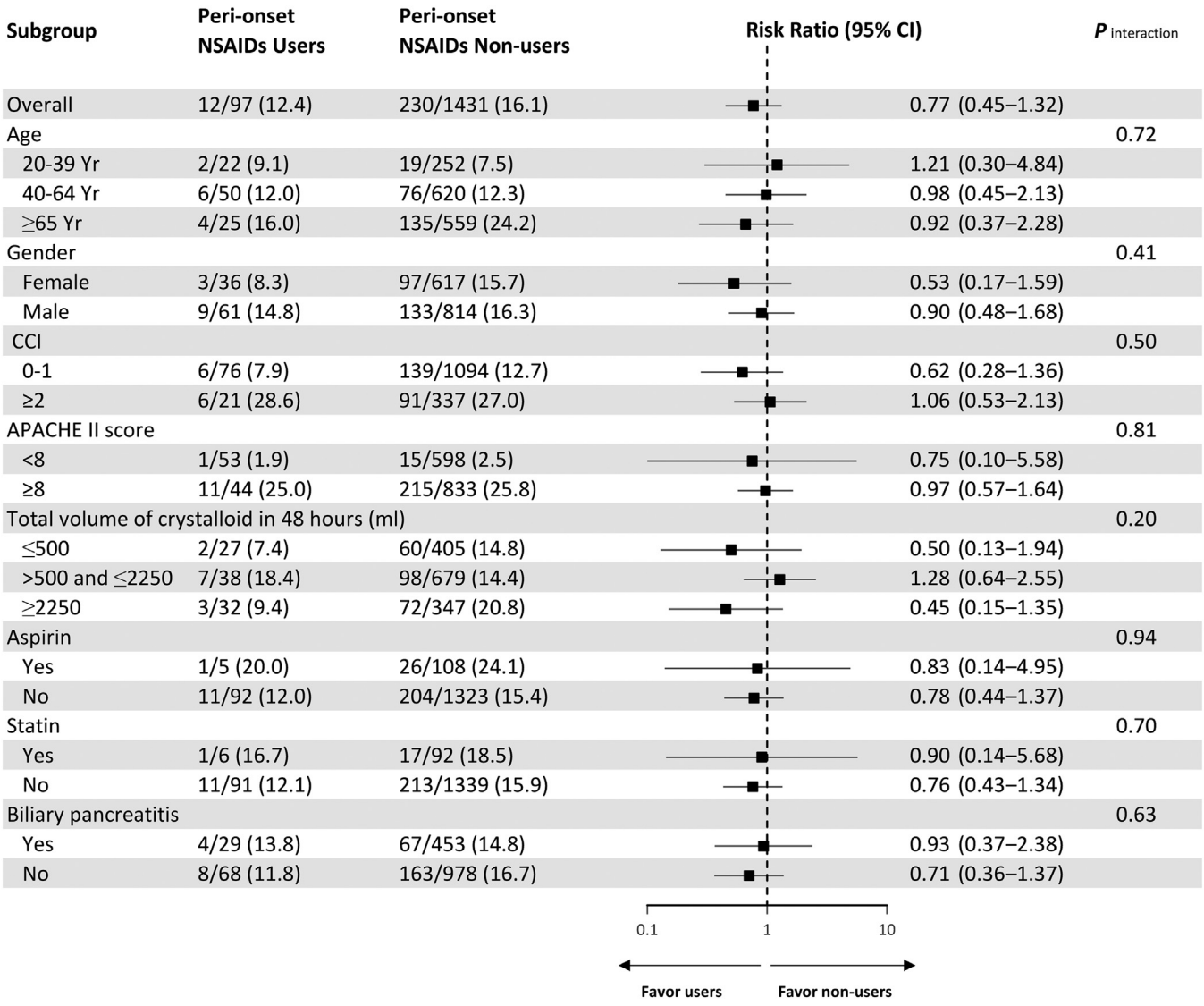

Fig. 1. Subgroup analysis on risk for organ failure. CCI, Charlson Comorbidity Index; APACHE II, Acute Physiology and Chronic Health Evaluation II.

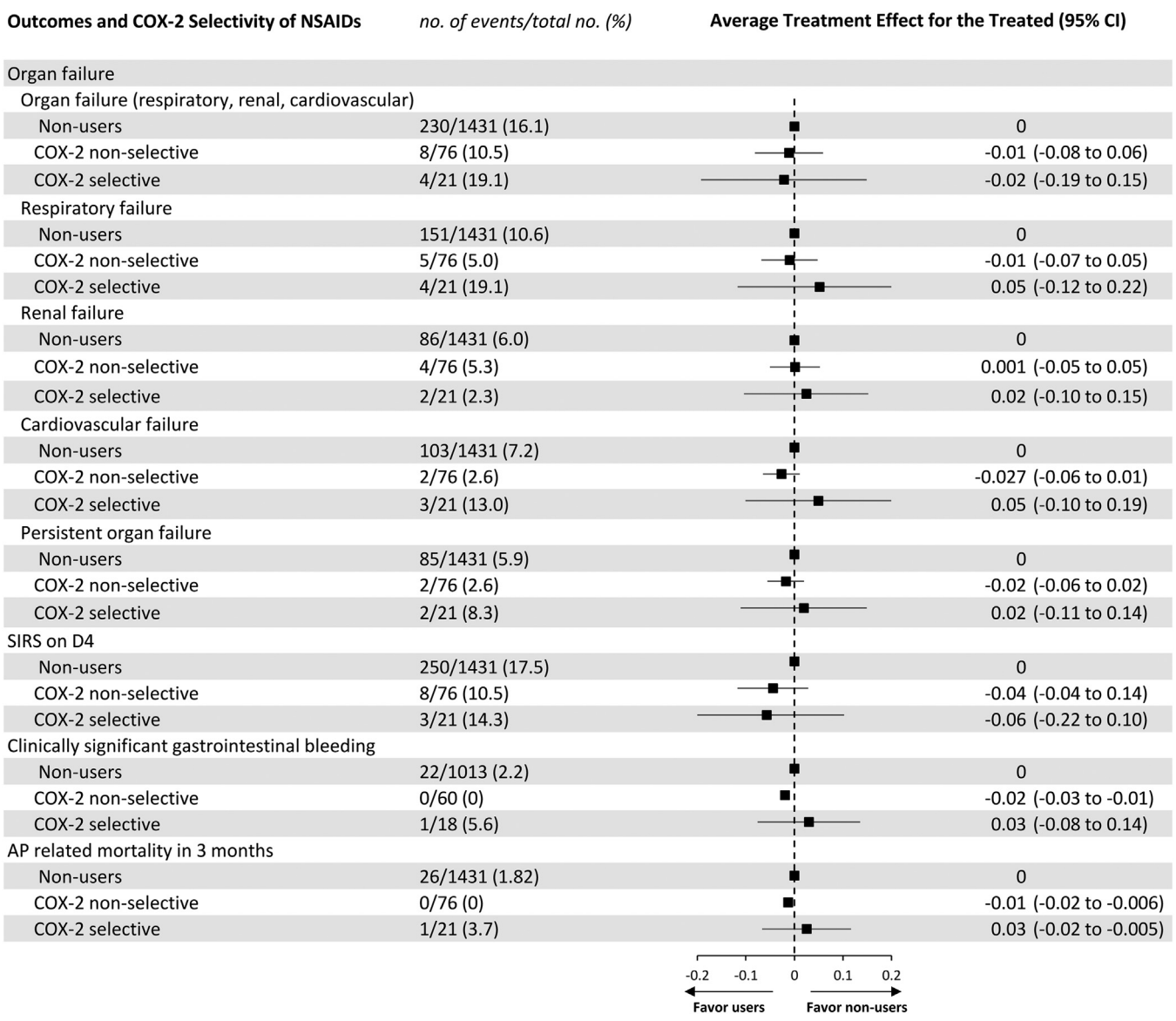

Fig. 2. The COX-2 selectivity of NSAIDs and outcomes. AP, acute pancreatitis; COX-2, cyclooxygenase-2; NSAIDs, non-steroidal anti-inflammatory drugs; SIRS, systemic inflammatory response syndrome.

compared with 10.5% in users of COX-2 non-selective NSAIDs (ATT, −0.01; 95% CI,

−0.08 to 0.06) and 19.1% in users of COX-2 selective NSAIDs (ATT, −0.02; 95% CI, −0.19 to 0.15). The risks of OF, persistent OF, renal, respiratory, and cardiovascular failure did not differ significantly depending on COX-2 selectivity and dose of NSAIDs (Fig. 2 and Fig. 3).

3.4. The NSAIDs use and SIRS

Among the 1528 patients with AP, 570 (37.3%), 261 (17.1%), and 849 (55.6%) patients developed SIRS on day 1, day 4, and within 7 days, respectively. In both propensity score-matched and inverse probability of treatment-weighted analyses, the proportion of patients with SIRS on day 1, day 4, and within 7 days were not significantly different between patients with and without peri-onset NSAIDs use (supplementary Table S3). SIRS scores were also not significantly different between patients with and without peri-onset NSAIDs from day 1 through day 7 (supplementary Figure S2). The difference between the maximal SIRS scores in 7 days and day 1 SIRS score also did not differ significantly between patients with and without peri-onset NSAIDs use (supplementary Table S3).

3.5. The statins or aspirin use and outcomes of AP

Among all patients with AP, 113 (7.4%) and 98 (6.4%) were aspirin and statins (i.e., rosuvastatin and atorvastatin) users. The risks of organ failure, persistent organ failure, ICU care during admission, AP-related mortality in 3 months, and clinically significant GI bleeding, did not differ between aspirin user and non-users in propensity score-matched and inverse probability of treatment-weighted analyses (Table S4). In propensity score-matched analysis, those who had used statins were less likely to develop respiratory organ failure (9.0% vs. 21.4%; RR, 0.42; 95% CI, 0.19 to 0.93) and persistent organ failure (3.4% vs. 12.4%; RR, 0.27; 95% CI, 0.08 to 0.98), while in inverse probability of treatment-weighted analysis, the results were insignificant across outcomes of AP (supplementary Table S5).

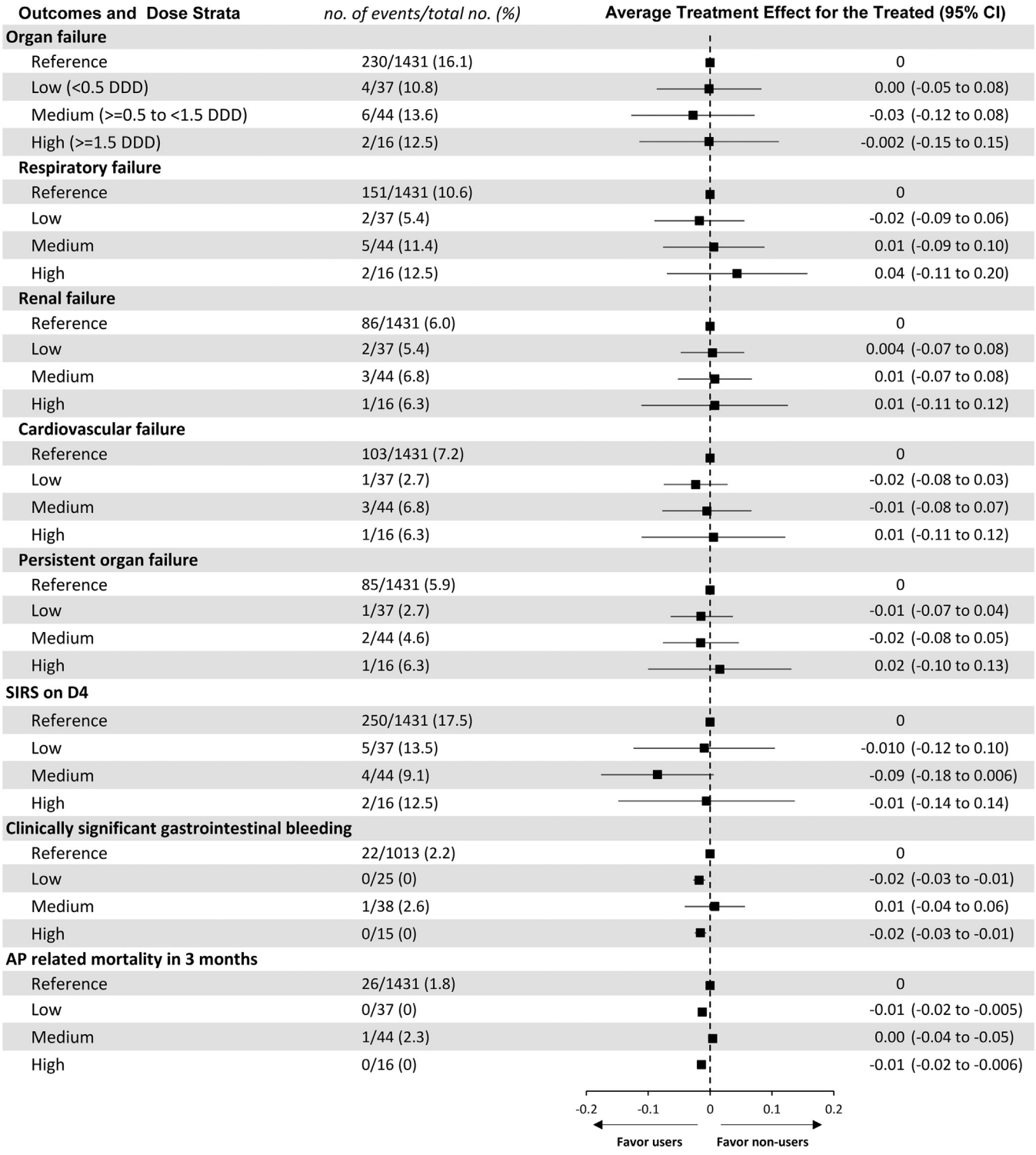

Fig. 3. The peri-onset NSAIDs dose and outcomes. AP, acute pancreatitis; DDD, daily defined dose; NSAIDs, non-steroidal anti-inflammatory drugs; SIRS, systemic inflammatory response syndrome.

4. Discussion

We investigated the real-world associations between peri-onset NSAIDs use and OF in patients with AP in this multicenter retrospective hospital-based cohort study, with adjustment for confounding by indication and consideration of COX-2 selectivity and dose of NSAIDs. The results showed no significant association between peri-onset NSAIDs use and the risk and severity of OF and SIRS in patients with AP within the first week, raising uncertainty regarding a clinically significant benefit in mitigating AP-induced OF with NSAIDs treatment.

Factors which influence the probability of NSAIDs use may also affect the occurrence of the outcomes and thus introduce bias (e.g., confounding by indication); therefore, controlling for confounding by indication is essential when NSAIDs treatment is not randomly allocated [19]. Propensity score-matched and inverse probability

of treatment-weighted analyses are the major statistical methods for controlling confounding by indication [20]. Both analyses attempt to balance the distributions of confounders between the two groups, with the propensity score-matched analysis matching patients with and without NSAIDs use according to the propensity score (probability of being treated with NSAIDs) and the inverse probability of treatment-weighted analysis weighting each patient by the inverse of the propensity score [21]. In this study we used both propensity score-matched and inverse probability of treatment-weighted analyses to adjust for confounding by indication, and the similarity between the results of the two analyses supported the veracity of our results.

Previous studies on the potential benefit of NSAIDs in patients with AP yielded mixed results. Vutipongsatorn et al. [22] found that NSAIDs use was not associated with a reduced risk of pancreatic necrosis. Furthermore, a randomized controlled trial comparing full-dose rectal diclofenac for 48 h and placebo found no significant difference between the two groups in the risk of SIRS and OF [23]. Although some retrospective studies reported that NSAIDs use was associated with reduced risks of pancreatic necrosis and pseudocysts [10], OF [2], and in-hospital mortality [2], those studies did not adjust for the imbalance in baseline characteristics between NSAIDs users and non-users. In the retrospective study with the largest case number, use of NSAIDs within 1 year before AP, regardless of the interval between the last dose of NSAIDs and the onset of AP, was associated with reduced OF and in-hospital mortality. Nonetheless, up to 95% of the participants in that study were male veterans, and no adjustment for confounding by indication was conducted [2]. By contrast, the participating hospitals in this study served the general public, and National Health Insurance covers inpatient and outpatient care for 99.8% of the population in Taiwan [24]. Therefore, the participants of this study should be representative of the general Taiwanese population with better generalizability. Moreover, we considered only individuals who had used NSAIDs within 3 days before and after presentation as having peri-onset NSAIDs use, as NSAIDs use before or after this time frame should have limited effects on the risk/severity of SIRS and OF within the first week of AP.

While COX-2 selective NSAIDs had been reported to reduce persistent OF in two studies, our analysis of real-world data found no significant benefit with COX-2 selective NSAIDs use. A previous study compared early treatment with COX-2 selective parecoxib and conventional treatment by propensity score-matched analysis found that parecoxib use was associated with reduced persistent OF in mild and moderately severe AP [25]. However, in that study the propensity score was calculated using not only baseline factors influencing the probability of NSAID use but also outcome measures, which should not be used for calculating the propensity score [26]. A randomized controlled trial [27] found that COX-2 selective NSAIDs for 10 days (parecoxib for 3 days followed by celecoxib for 7 days) in patients predicted to have severe AP reduced C-reactive protein level, SIRS, and persistent OF. However, that study excluded patients with cardiac, renal, and pulmonary diseases, and such patients are at increased risk of NSAIDs-related adverse events and represent a sizable patient population. The risk-benefit ratio of prolonged NSAIDs treatment in broad patient populations should be further studied.

Acetylsalicylic acid and statins were proposed to be associated with reduced morbidity in AP [10,28], although the association was not consistent [29]. Our results did not support the beneficial effect of prior aspirin on severity of AP; on other hand, prior use of statins may be associated with reduced respiratory organ failure and persistent organ failure in those who might be clinically indicated for statin use, as supported by propensity score-matched analysis in this study. Well-designed randomized controlled trials to confirm the efficacy of statins in optimal subgroups are warranted [30].

This study comprehensively analyzed the occurrence of SIRS and serial changes in SIRS score which reflects the magnitude of systemic inflammatory response and represents an important surrogate for OF in AP [7]. The findings that peri-onset NSAIDs use was not associated with reduced risk and severity of SIRS further supported that NSAIDs treatment provides no significant protection against OF in AP. Animal studies examining the effects of NSAIDs on the severity of AP also yielded mixed results [31], with some reporting benefits while others showing no benefits and even increased fat necrosis with NSAIDs treatment [32]. The effects of NSAIDs on the systemic inflammatory reaction and clinical outcomes are likely complex and heterogenous and warrant further study. Future clinical research needs to focus on higher doses of NSAIDs and NSAIDs treatment in predicted moderated severe/severe AP since we did not find clinical benefits of relatively low-dose NSAIDs in population with milder disease (i.e., disease with medium APACHE II score of 7 in NSAIDs users).

Our study had several strengths. We used propensity score-matching and inverse probability of treatment-weighted analysis to account for potential bias resulted from the imbalance in baseline characteristics, and both analyses found no significant benefit with peri-onset NSAID use. Second, the study population included patients from all levels of healthcare and those with pre-existing conditions; therefore, the results should have better generalizability. Last, the prospectively maintained NTUH-iMD dataset which integrated all electronic medical records and the administrative data of Taiwanese single-payer healthcare system enabled comprehensive ascertainment of a wide range of outcomes and differentiation between new-onset and existing OF.

This study had limitations. First, only 6.3% of patients had peri-onset NSAIDs use, raising the possibility of inadequate statistical power and type II error. Nevertheless, under the assumption of a risk ratio of 0.5 for NSAIDs use in relation to organ failure, the statistical power increased to 87% when broadening the definition of NSAIDs use to incorporate prior aspirin use in the sensitivity analysis. Importantly, this modification yielded consistent result. Taken together, our results suggested that the potential benefit of NSAIDs might not be as significant as reported previously and thus a future trial with adequate statistical power is warranted. Second, although information on NSAIDs prescribed in other institutions was also available in the electronic medical records and included in the analysis, information on over-the-counter NSAIDs was not available if patients did not report such information during admission. However, the use of over-the-counter NSAIDs, of which the prevalence data is absent in Taiwan, should be much less prevalent compared with other areas given that universal health insurance coverage and easy access to healthcare reduced the use of over-the-counter NSAIDs. Third, the dose of NSAIDs used in this study was lower than that in the randomized controlled trial [27] which reported benefits with high-dose NSAIDs use for 10 days in patients with predicted severe AP; therefore, the possibility of potential benefit or adverse effects with prolonged high-dose NSAIDs treatment for patients with more severe AP could not be excluded based on our results. Furthermore, this study identified the research population with ICD-9 and ICD-10 codes, which was found to have suboptimal positive predictive value of 0.71 [33]. Despite suspicion of imprecise identification of AP, this study did exclude 21.9% patients who had neither enzymatic nor imaging criterion of new-onset AP (Figure S1), strengthening the accuracy of diagnosis in included population. Finally, unspecified etiologies of AP, which were identified in 40% of patients, limited our effort to clarify the influence of NSAIDs in subgroup analysis.

In conclusion, peri-onset NSAIDs use was not associated with a reduced risk of OF and persistent OF after the onset of AP in this retrospective study. Prior use of statins was associated with reduced risk of respiratory failure and persistent organ failure during acute pancreatitis in those for whom statin use had been clinically indicated.

Ethics

The study was approved by National Taiwan University Hospital Research Committee (202009074RIND).

Given the electronic data were all de-identified in the academic hospital-based database, individual informed consent was not required according to Taiwan's Human Subject Research Act.

Financial Support

This study received financial support from Department of Medical Research of National Taiwan University Hospital and National Taiwan University Cancer Center (NTUCCS-111-18).

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to express thanks to the staff of Department of Medical Research for providing clinical data from National Taiwan University Hospital-integrative Medical Database (NTUH-iMD). The authors also thank Yi-Chang Chou for technical assistance in graph production. We express our deeply appreciation to Chieh-Chan Chen in National Taiwan University Hospital (Taipei, Taiwan), Ji-Yuh Lee, Yu-Jen Fang, and Hau-Jyun Su in National Taiwan University Hospital, Yun-Lin Branch (Yunlin, Taiwan), and Wen-Hao Hu, Min-Horn Tsai in National Taiwan University Hospital, Hsin-Chu Branch (Hsinchu, Taiwan) for their contribution to acquisition of data.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2023.12.010.

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