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The incidence of new mental health disorders after acute pancreatitis: A large, propensity-matched, observational study

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ABSTRACT

Introduction: The prevalence of acute pancreatitis (AP) and mental health disorders (MHDs) are rising. While the association between chronic pancreatitis (CP) and MHDs is established, it is unknown whether there is a risk of MHDs after an index episode of AP. The aim of this study was to evaluate the incidence of MHDs and pharmacotherapy use after an episode of AP.

Methods: This was a large observational study using the TriNetX research network, an electronic health record dataset containing inpatient and outpatient data from more than 50 healthcare organizations. Patients with AP from 2015–2020 were identified. Four cohorts were created: acute necrotizing pancreatitis (ANP), acute pancreatitis without necrosis (AP-WON), acute appendicitis, and healthy controls without pancreatitis. The cohorts were matched by age, sex, race, ethnicity, and nicotine and alcohol use. The primary outcome was new composite MHDs at one-year. Secondary outcomes included stratified MHDs, psychiatric medication use, opioid analgesic use, and all-cause mortality.

Results: The ANP, AP-WON, appendicitis, and healthy control cohorts contained 11,806, 177,266, 27,187, and 561,833 patients, respectively. Patients with AP-WON had significantly higher rates of composite MHDs compared with those hospitalized for appendicitis (9.7% vs 4.7%, HR 1.9, 95% CI 1.7–1.9). This association was augmented when comparing ANP to appendicitis (12.8% vs 5.2%, HR 2.4, 95% CI 2.1–2.7). All secondary outcomes were observed at significantly higher rates in the AP-WON cohort when compared to appendicitis. Again, these associations were augmented comparing ANP to appendicitis.

Conclusion: Compared with controls, patients with AP had significantly higher rates of new MHDs and their associated pharmacotherapies at one-year, suggesting that a single episode of AP may independently place patients at risk for developing MHDs irrespective of whether they go on to develop CP.

1. Introduction

Acute pancreatitis (AP) is the most common gastrointestinal disease requiring inpatient hospitalization, with an annual incidence of 34 per 100,000 people in developed countries [1]. Although the short-term disease course of AP is often self-limiting, emerging data have associated AP with numerous long-term complications, including diabetes, pancreatic exocrine insufficiency, chronic liver disease, and osteoporosis [2–4]. Concomitantly, mental health disorders (MHDs) are exceedingly common and are increasing in prevalence at rapid rates [5].

The association between MHDs and chronic pancreatitis (CP) has been well described in prior observational studies [6–12]. CP, a condition associated with chronic pain, poor health-related quality of life (HR-QOL), and exocrine insufficiency, has also been associated with high rates of opiate use and abuse [13–18]. Moreover, there are also early data to suggest a genetic link to severe pain and MHDs in patients with CP [9,10]. While these data have shed light on the concerning association between MHDs and CP, there is little understanding as to whether this association takes hold prior to the development of overt CP. More specifically, data regarding the development of new-onset MHDs after an episode AP are scarce. Therefore, the primary aim of this study, using a large, electronic health record (EHR)-derived national dataset, was to evaluate the cumulative incidence of new-onset MHDs at one-year following an

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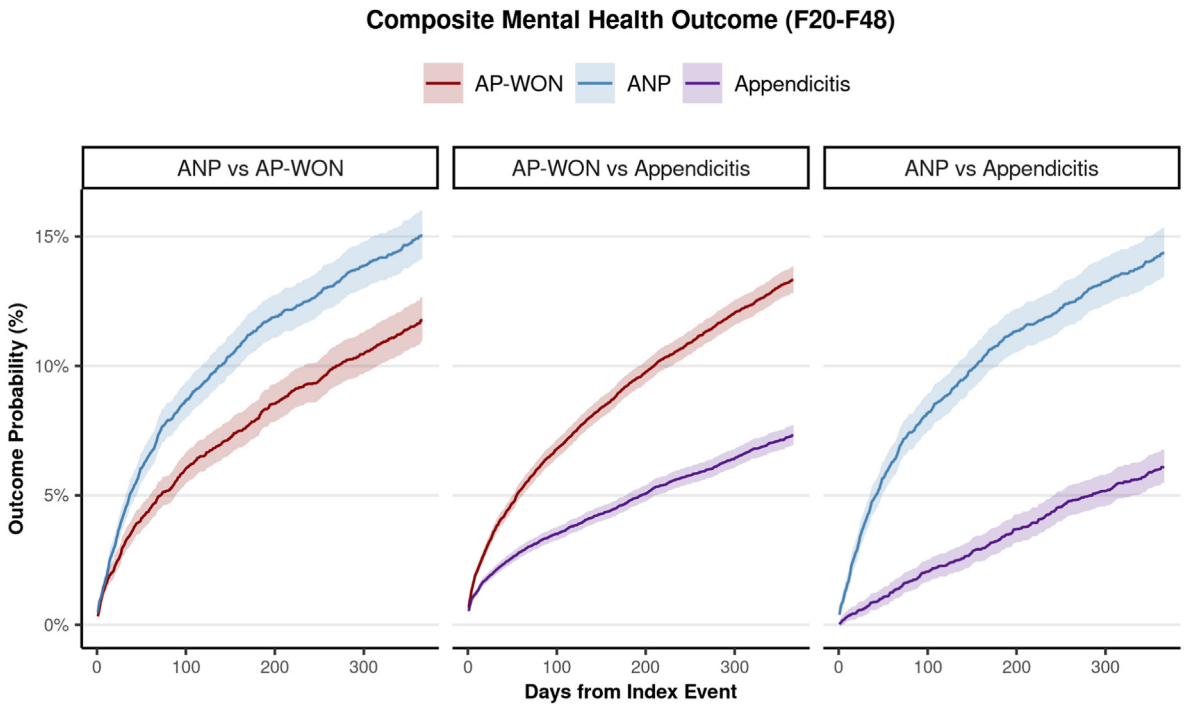

Fig. 1. Kaplan-Meier Analyses of composite mental health outcome (F20–F48). ANP: Acute necrotizing pancreatitis. AP-WON Acute pancreatitis without necrosis.

episode of AP. Secondary aims included analyzing the incidence of new onset selective serotonin reuptake inhibitor (SSRI), oral opioid analgesic (OOA), and benzodiazepine use, as well as all-cause mortality at one-year after AP.

2. Methods

2.1. Cohort selections

The study utilized data obtained from TriNetX, a federated network of deidentified electronic health record data from more than 50 healthcare organizations and comprising more than 80,000,000 patient lives. Four separate patient cohorts were identified for analysis. All cohorts had an index event occurring between October 1, 2015 and December 31, 2020. The four cohort index events were acute necrotizing pancreatitis (ANP), acute pancreatitis without necrosis (AP-WON), acute appendicitis, and healthy controls without AP. To ensure the healthy control cohort was active within the EHR dataset during the study period, the search criteria included those presenting for a routine outpatient medical visit in which a serum lipid panel was performed, and who underwent a screening exam for cervical, colorectal, or breast cancer. To optimize the ease of the analyses, the healthy control and acute appendicitis cohort sizes were attenuated by selecting those presenting during the period of July 1, 2017–December 31, 2020, and January 1, 2018–December 31, 2020, respectively. The specific criteria used to define these four cohorts are presented in the **Supplemental Material**. All cohorts were queried to exclude those that had the primary or secondary outcomes prior to the onset of pancreatitis. These exclusions are presented in the **Supplemental Material**. Initial cohort sizes are described using the number of patients identified from the initial query.

2.2. Outcomes

The primary outcome of interest was the new onset of a composite mental health outcome. This composite outcome consisted of the F20–F48 international classification of diseases (ICD)-10 diagnostic codes for schizophrenia and other non-mood psychotic disorders, mood disorders (e.g. major depressive disorder), and anxiety disorders, and stratified these categories according to previously published data from psychiatric literature using TriNetX [19,20]. Secondary outcomes included the incidence of three mental health disorder categories in isolate (ICD-10 codes F20–29, F30-39, and F40-48), new-onset oral opioid analgesic (OOA), selective serotonin reuptake inhibitor (SSRI), and oral benzodiazepine use, and all-cause mortality. To assess new-onset outcomes only, patients with the outcome prior to the index event (e.g. on SSRI before acute pancreatitis) were excluded during the propensity matched analysis, and not at the point of cohort identification.

2.3. Propensity matching and statistical analyses

As these are cohort-level data, propensity matching was utilized to match the cohorts for analyses. The cohorts were matched based on age, sex, gender, race, ethnicity, and alcohol and nicotine use. Using logistic regression, propensity scores were generated for each patient within each cohort. Matching was performed using a 1:1 greedy nearest neighbor algorithm with a caliper width of 0.1 pooled standard deviations. Standardized mean differences (SMD) < 0.1 were considered well-balanced covariates. Kaplan-Meier statistics were used to assess the rate of outcomes during the 365-day follow-up period after the onset of pancreatitis. Comparisons between the cohorts were performed using log-rank tests. Hazard ratios (HR) were created using a proportional hazard model as described previously [20]. HRs are reported with corresponding 95% confidence intervals (CI). For each outcome, patients from each cohort that experienced the particular outcome prior to the index event, were excluded from the analysis. Kaplan-Meier graphical curves were fashioned with R 4.1.3 (The R Foundation)using the disparate data outputs for the TriNetX Kaplan-Meier statistics. The ggplot2 3.3.5, ggfortify 0.4.14, and Tidyverse 1.3.1 packages were employed in graphics generation. Additional analyses comparing outcome rates at one year (e.g. all-cause

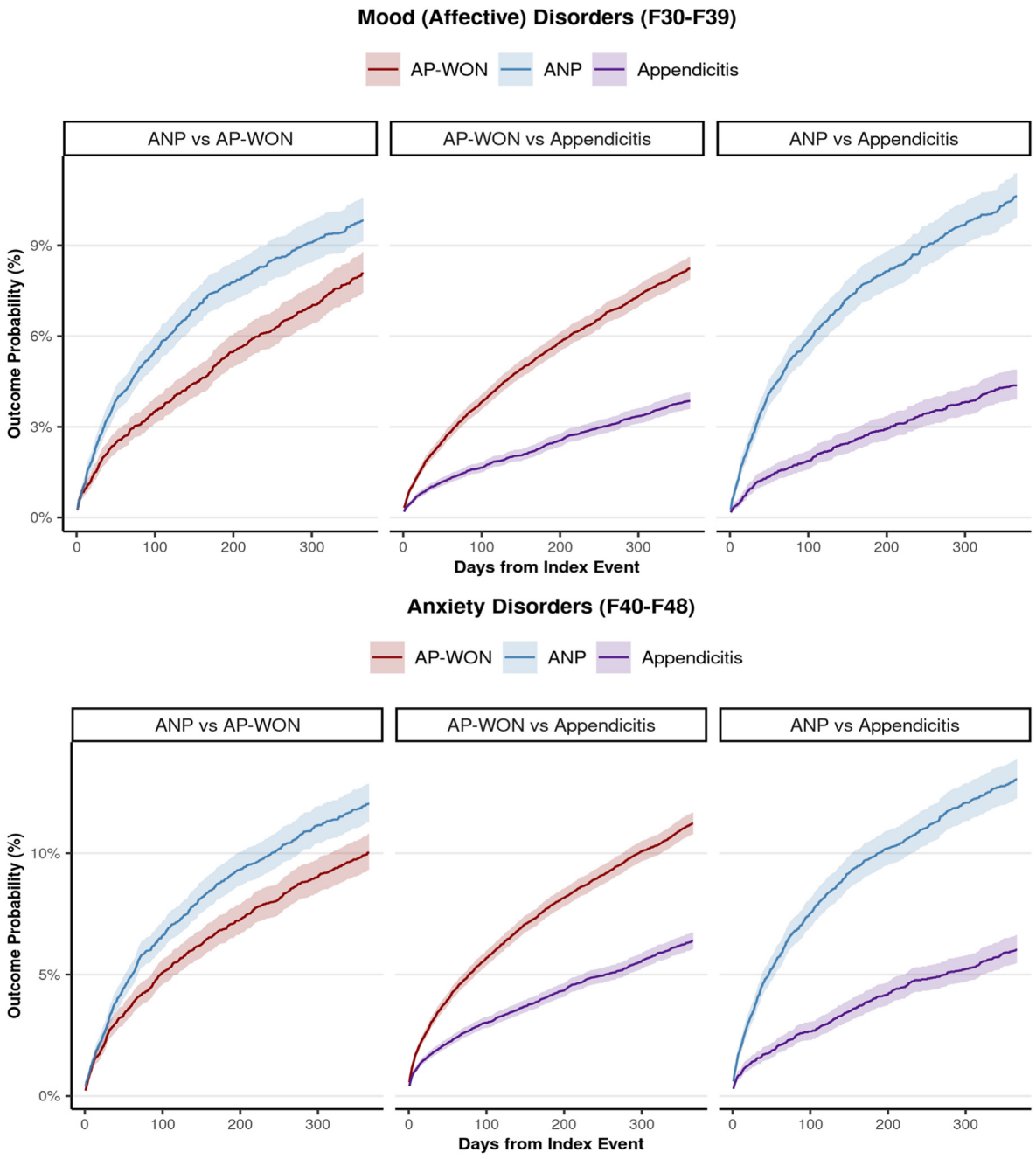

Fig. 2. Kaplan-Meier Analyses of mood disorders. ANP: Acute necrotizing pancreatitis. AP-WON Acute pancreatitis without necrosis.

mortality) were performed with Fisher's exact and Chi-squared tests, where appropriate, and reported as odds ratios (OR) with 95% CI. TriNetX rounds cohort event rates to 10 if the absolute number is < 10 to augment anonymity and therefore, outcomes with low event rates (≤1% of the total cohort), were not included for analysis. All analyses were performed within the TriNetX user interface. Details regarding statistical tests and systems utilized by TriNetX in these analytics is described in detail elsewhere [20].

3. Results

3.1. Patient cohorts and baseline characteristics

From October 1, 2010 to December 31, 2020, 66,570,555 patients had at least one clinical encounter. The healthy control cohort consisted of 25,967,739 individuals during the entire study period. Using the truncated time range to attenuate this group, a cohort of 561,833 controls remained. The initial sizes for the ANP,AP-WON, and acute appendicitis cohorts were 11,806, 177,266, and 27,187, respectively. The overall 11-year disease prevalences were 18/100,000 for ANP and 266/100,000 for AP-WON. Due to the routine cancer screening criteria used to define controls, this unmatched cohort contained 71% women. Nicotine and alcohol use was also seen at lower rates in the controls. Baseline characteristics of the unmatched patient cohorts are presented in the **Supplemental Material**.

3.2. Acute necrotizing pancreatitis versus acute pancreatitis without necrosis

Two matched cohorts of 11,876 patients were used to compare

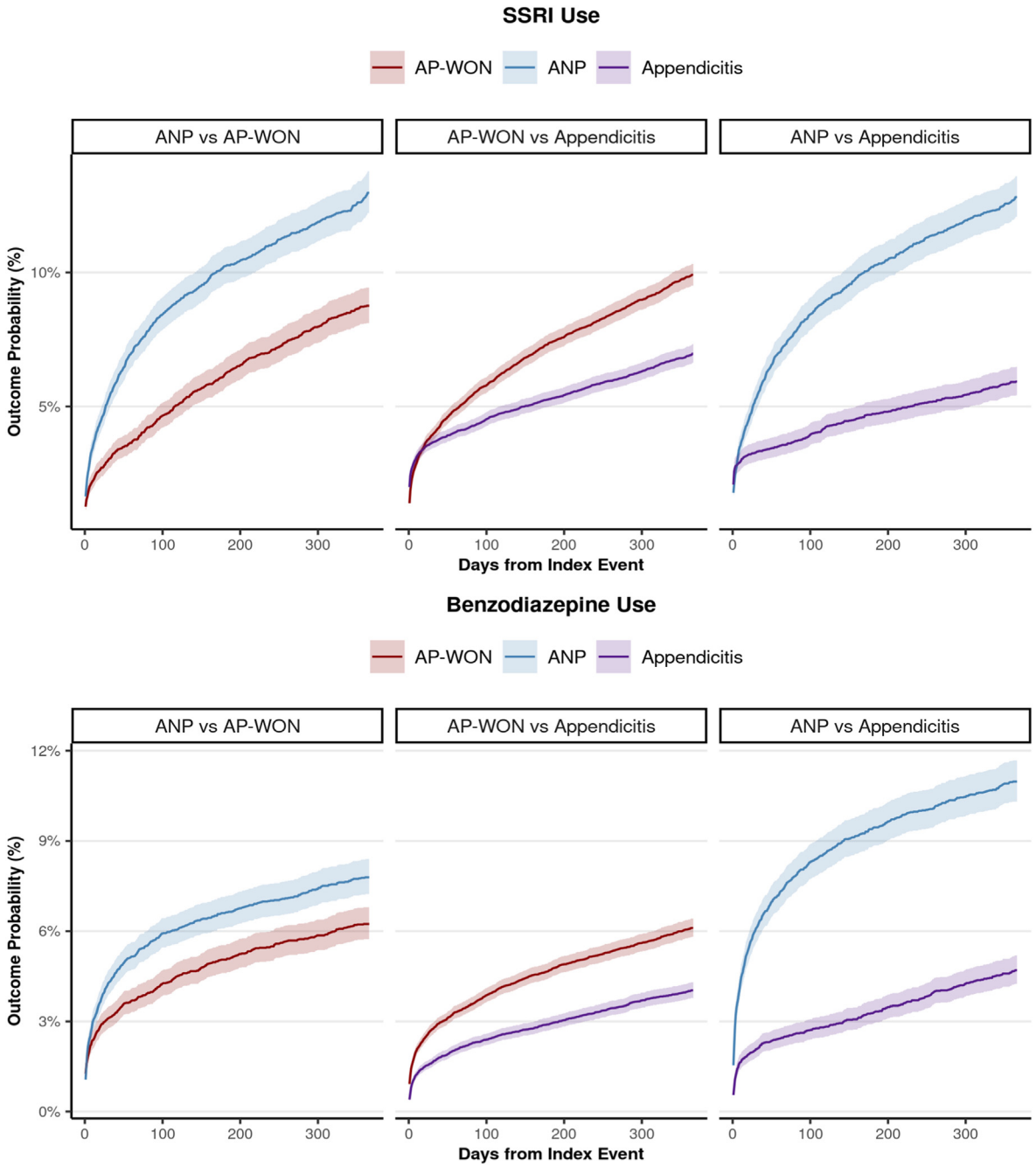

Fig. 3. Kaplan-Meier Analyses of SSRI and oral benzodiazepine use. ANP: Acute necrotizing pancreatitis. AP-WON Acute pancreatitis without necrosis.

outcomes between ANP and AP-WON. The ANP cohort had higher rates of the primary composite mental health outcome compared with the AP-WON cohort (HR 1.2, 95% CI 1.10–1.34) (Fig. 1). Similarly, both mood disorders and anxiety disorders were also more likely associated with the ANP cohort (Fig. 2). There was no significant difference in new-onset non-mood psychotic disorders (Supplemental Material). New SSRI (HR 1.6, 95% CI 1.40–1.72), benzodiazepine (HR 1.3, 95% CI 1.17–1.48), and OOA use (HR 1.3, 95% CI 1.17–1.37) were all more common in the ANP cohort (Fig. 3). One-year all-cause mortality was 9.52% in the ANP group and 5.57% in the AP-WON group (OR 1.8, 95% CI 1.61–1.97) (Fig. 4, Supplemental Material). *Acute Necrotizing Pancreatitis versus Acute Appendicitis*.

Two matched cohorts of 11,630 were analyzed. There was a very slight prominence of alcohol use disorder in the ANP cohort (SMD 0.106), but all other covariates were well matched (Table 1). The ANP group had significantly higher rates of the composite mental health outcome (HR 2.4, 95% CI 2.1–2.7) (Fig. 1) as well as all other secondary outcomes (Figs. 2–4, Supplemental Material). All-cause mortality at one-year was 9.9% in the ANP cohort and 3.3% in the appendicitis cohort (HR 2.9, 95% CI 2.5–3.2) (**Supplemental Material**).

3.3. Acute pancreatitis without necrosis versus acute appendicitis

Two cohorts of 35,196 patients resulted from the matching process. All covariates were well matched. The primary outcome of

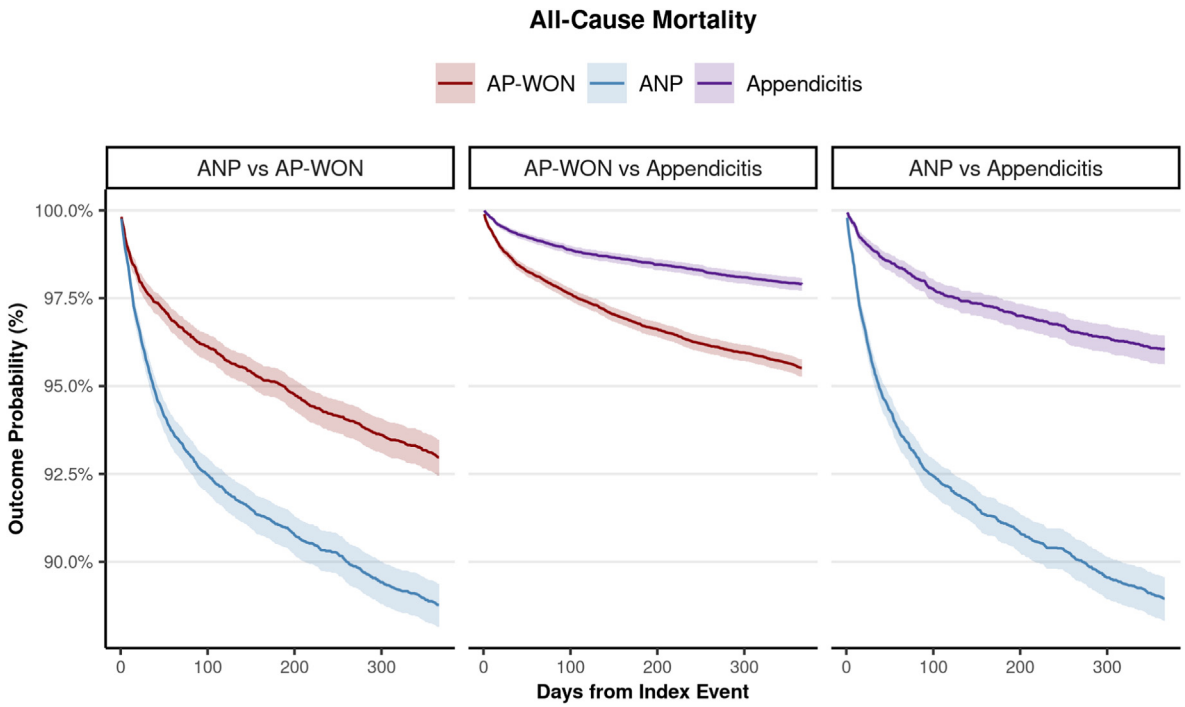

Fig. 4. Kaplan-Meier Analyses of all-cause mortality. ANP: Acute necrotizing pancreatitis. AP-WON Acute pancreatitis without necrosis.

composite mental health disorders was significantly higher at one-year in the AP-WON cohort (HR 1.9, 95% CI 1.74–1.99) (Fig. 1). Though attenuated compared with the ANP cohort, all secondary outcomes were significantly higher in the AP-WON cohort compared with the acute appendicitis cohort (Figs. 2–4, Supplemental Material).

3.4. Acute necrotizing pancreatitis versus healthy controls

After matching, both the ANP and healthy control cohorts contained 11,225 patients. The covariates of age (ANP mean age 52.6 ± 16.8 years and control mean age 54.6 ± 15.1 years, SMD 0.13) and alcohol use disorder were sub-optimally matched, however, the healthy control cohort contained the higher proportion of alcohol use-disorder patients (14.3% vs 19.2%, SMD 0.13) (Table 1). The ANP group had a significantly higher risk of the composite mental health outcome (HR 2.7, 95% CI 2.34–2.99), as well as all secondary outcomes aside from non-psychotic mood disorders alone (Fig. 2, Supplemental Material). One-year all-cause mortality was 9.6% in the ANP cohort, and 0.7% in controls (OR 14.2, 95% CI 11.34–17.79) (Fig. 4, Supplemental Material).

4. Discussion

Over the past 20 years, the incidence and hospitalization rates of AP have been steadily rising in developed countries [21]. Additionally, concomitant increases in the worldwide incidence of MHDs have also been described [22]. In the United States alone, an estimated 8400/100,000 persons have depression, markedly higher than the global incidence of 3153/100,000 persons [22]. In addition to being prevalent, AP and MHDs are of importance as they can affect people of all ages. Both recent trends in isolate are concerning, however any potential link between the two has yet to be well examined. The development of MHDs has previously been associated with chronic gastrointestinal diseases including hepatic cirrhosis, irritable bowel syndrome, and inflammatory bowel disease [23–30]. Furthermore, the relationship between CP and various MHDs has been heavily examined, with several studies showing significant associations between CP and the development of major depressive and anxiety disorders [6,9–12]. It is known that most cases of CP develop in patients with known histories of AP or recurrent acute pancreatitis (RAP) [31–34]. Despite this knowledge, little data exist regarding the incidence of MHDs after AP – regardless of the future development of CP. We aimed to close this gap by examining various psychosocial outcomes at one year after an episode of AP. The present study, using four large propensity-matched cohorts, demonstrates a strong association with acute pancreatitis and the one-year incidence of MHDs compared with controls. Moreover, this study also shows that this association is higher in patients with ANP – i.e. those with more severe disease – compared with AP-WON. Beyond MHDs, patients with AP also were shown to have higher rates of new onset OOA, SSRI, and oral benzodiazepine use compared with controls at one year.

Our results demonstrate that a single episode of AP was associated with a greater than two-fold increase in the one-year incidence of MHDs compared with matched controls. Nearly 10% of patients had a new MHD diagnosed within the year after an episode of AP. This finding was primarily driven by the F30–F39 mood disorders (e.g. major depressive disorder) and F40–F48 anxiety disorders, with absolute one-year incident rates of 6.3% and 7.3%, respectively in the AP-WON cohort (**Supplemental File**). In parallel, the validity of these findings are supported by observed increases in new SSRI and oral benzodiazepine usage. Patients with AP had nearly a three-fold increase in SSRI use and a greater than seven-fold increase in oral benzodiazepine use, compared with matched controls. These findings expand on the existing knowledge that has defined the relationship between MHDs and CP [6,9–12].

It can now be suggested that for some patients, the risk of developing a MHD may be augmented after a single episode of AP, well before the development of RAP or CP. This finding is important for several reasons. First, those providing routine care for patients after AP may be more diligent in offering routine screening for

Table 1
Covariates used for Propensity Matching and Results.

	AP-WON vs Non-Pancreatitis Control			ANP vs Non-Pancreatitis Control			AP-WON vs Appendicitis			ANP vs Appendicitis			ANP vs AP-WON		
	AP-WON	HC	SMD, p-value	ANP	HC	SMD, p-value	AP-WON	Appendicitis	SMD, p-value	ANP	Appendicitis	SMD, p-value	ANP	AP-WON	SMD,p-value
Matched Cohort Sizes	234,768			11,225			35,196			11,630			11,876		
Age (mean ± SD)	55.1 ± 17.5	56.2 ± 14.5	0.07 < 0.01	52.6 ± 16.8	54.6 ± 15.1	0.13 < 0.01	37.0 ± 21.6	36.8 ± 21.7	0.007 0.30	51.3 ± 17.6	52.9 ± 18.2	0.08 < 0.01	51.7 ± 17	51.7 ± 17	0.00 0.91
Women	136,516 (58.1)	138,433 (58.1)	0.01 < 0.01	4535 (40.4)	4587 (40.9)	0.010.48	17,364 (49.3)	17,086 (48.5)	0.02 0.03	4650	4704	0.01 0.47	4581 (38.6)	4582 (38.6)	<0.01 0.99
Race															
White N (%)	161,438(68.8)	156,481 (66.7)	0.05 < 0.01	7538 (67.1)	7246 (64.6)	0.05 < 0.01	23,383 (66.4)	24,108 (68.5)	0.01 0.30	8509	8673	0.03 0.01	7770 (65.4)	7784 (65.5)	0.00 0.85
Black or African American N (%)	39,460 (16.8)	36,688 (15.6)	0.03 < 0.01	1465 (13.1)	1421 (12.7)	0.01 0.38	3179 (9.0)	3190 (9.1)	0.001 0.89	1397	1364	0.01 0.50	1503 (12.7)	1497 (12.6)	0.00 0.91
Asian N (%)	4605 (1.9)	4076 (1.7)	0.02 < 0.01	147 (1.3)	121 (1.1)	0.02 0.11	1102 (3.1)	998 (2.8)	0.02 0.02	159	148	0.01 0.53	149 (1.3)	139 (1.2)	0.01 0.55
American Indian or Alaska Native N (%)	794 (0.3)	1056 (0.5)	0.02 < 0.01	67 (0.6)	66 (0.6)	0.00 0.93	146 (0.4)	178 (0.5)	0.01 0.07	93	82	0.01 0.40	76 (0.6)	56 (0.5)	0.02 0.08
Native Hawaiian or Other Pacific Islander N (%)	286 (0.1)	330 (0.1)	0.01 < 0.01	10 (0.1)	12 (0.1)	0.01 0.67	100 (0.3)	95 (0.3)	0.0020.72	13	11	0.01 0.68	10 (0.1)	10 (0.1)	<0.01 1.00
Unknown Race N (%)	28,185 (12.0)	36,137 (15.4)	0.10 < 0.01	1998 (17.8)	2359 (21.0)	0.08 < 0.01	7286 (20.7)	6627 (18.8)	0.04 < 0.01	1459	1.352	0.030.03	2368 (19.9)	2393 (20.2)	0.01 0.69
Ethnicity															
Not Hispanic or Latino N (%)	154,859(65.9)	153,072 (65.2)	0.02 < 0.01	8117 (72.3)	8055 (71.8)	0.010.36	20,015 (56.9)	19,610 (55.7)	0.02 < 0.01	7509	7810	0.05 < 0.01	8581 (72.3)	8583 (72.3)	0.00 0.98
Hispanic or Latino N (%)	19,483 (8.3)	23,086 (9.8)	0.05 < 0.01	1077 (9.6)	1105 (9.8)	0.010.53	5004 (14.2)	5093 (14.5)	0.01 0.33	1059	1049	0.003 0.82	1171 (9.9)	1167 (9.8)	0.00 0.93
Unknown Ethnicity N (%)	60,426 (25.7)	58,610 (24.9)	0.02 < 0.01	2031 (18.1)	2065 (18.4)	0.010.56	10,177 (28.9)	10,493 (29.8)	0.02 < 0.01	3062	2771	0.06 < 0.01	2124 (17.9)	2126 (17.9)	0.00 0.97
Substance Use															
Nicotine Dependence N (%)	31,247 (13.3)	35,412 (15.1)	0.05 < 0.01	2066 (18.4)	2346 (20.9)	0.06 < 0.01	2882 (8.2)	2855 (8.1)	0.002 0.71	1848	1692	0.04 < 0.01	2352 (19.8)	2350 (19.8)	0.00 0.974
Alcohol Related Disorders N (%)	11,311 (4.8)	14,084 (6.0)	0.05 < 0.01	1608 (14.3)	2152 (19.2)	0.13 < 0.01	856 (2.4)	866 (2.5)	0.002 0.81	1159	815	0.106 < 0.01	2053 (17.3)	2049 (17.3)	0.00 0.95

MHDs, especially for those with additional risk factors such as substance abuse, or a family history of MHDs. In the Kaplan-Meier analyses, the difference in the incidence of new MHDs between patients with AP and controls diverges most significantly in the first 120 days (Figs. 1 and 2), reiterating the importance of recognizing this association immediately after an episode of AP. Second, early data have identified genetic links between pancreatitis-related pain and major depression [9,10]. While this observation applies to those with CP, it is plausible that unrecognized major depression could worsen pain during and after an episode of AP. Recognizing and treating an occult MHD early, may offer an opportunity to mitigate OOA usage in these circumstances, which has several immediate and long-term benefits [13–18,35–37].

The severity of AP appears to be of significance in the onset of MHDs after AP. As these are aggregate cohort data, were unable to assess AP disease severity using prognostic scores [38,39]. We therefore chose to stratify disease severity based on the ICD-10 coded presence of necrosis. While there are certainly exceptions to the rule, in general, patients with ANP have more severe, complicated, and longer disease courses than those with AP-WON [40,41]. The validity of stratifying disease severity by the presence of necrosis is supported by the significantly higher all-cause mortality seen in the ANP group compared with the AP-WON group (9.5% vs 5.6%, $p < 0.001$) (**Supplemental Material**). We elected not to censor patients with more severe AP-WON (eg those with end-organ damage) and instead include the entire spectrum of patients. This was due in part to the argument that the ANP cohort also contains patients with milder ANP (eg small volume, self-limiting necrosis without end-organ damage) and therefore comparing the entire spectrum of both cohorts minimizes systematic biases rather than the strategy of censoring severe AP-WON and mild ANP. Comparing patients with ANP and AP-WON, those with ANP had moderate, but significantly higher rates of all outcomes, aside from non-mood psychotic disorders, which were overall low-incidence events. In addition to the longer and more severe disease courses seen in ANP in general, the heightened risk of new MHDs in ANP patients could be influenced by several unmeasured covariates that occur at higher rates in ANP, including invasive drainage procedures, prolonged hospitalizations, the need for critical care services – including mechanical ventilation, and the development of exocrine pancreatic insufficiency.

Our study has several limitations that need to be acknowledged. The nature of aggregate data limits the ability to conduct more complex and granular analyses. However, it has been established that results obtained from aggregate data can provide high quality and applicable evidence for large datasets [42]. The utilization of aggregate data also does not permit for multivariable analyses, thus we utilized propensity matching and compared the 4 cohorts independently in a univariate fashion. We chose to match the cohorts by age, race, ethnicity, and sex, as well as smoking and alcohol use, both of which are directly associated with pancreatitis and MHDs [43–47]. We were unable to quantify alcohol and nicotine use at a patient level and relied on ICD-10 codes for nicotine and alcohol dependence. It is possible that there are unmeasured covariates which were not matched for that could have impacted the results. Additionally, as this is an EHR-derived dataset, we were unable to verify the accuracy of the coded information which could potentially impact our results. It is also exceedingly difficult to ensure that complete information regarding outpatient medications were obtained from pharmacies outside of the TriNetX network. Moreover, there may be instances when a medication that is coded for is not actually being taken by a patient. Hence, it is possible that true medication rates may be underestimated. To ensure the healthy control cohort was active during the study period, we chose to define this as individuals who participated in routine, age-appropriate cancer screening or health maintenance. Our definition, which uses cervical, colorectal, and breast cancer screening, has the potential of skewing the age and sex distribution of the healthy control group and introducing additional biases inherent to a healthy population that is proactive in healthcare maintenance. Despite this, we felt it important to define controls as those that were actively participating in routine health maintenance. To combat against systematic biases introduced by this healthy proactive cohort, we also formed a second control group of patients hospitalized with acute appendicitis. This control group is more similar to the pancreatitis cohorts as they required hospitalization and therefore, eliminates confounding of the outcomes associated with the independent variable of being hospitalized. While the SMD values for age were slightly >0.1 for the ANP and AP-WON comparisons against healthy controls, the absolute difference in mean age for those two comparisons was 2 years or less for both (Table 1). The cohorts were otherwise well-matched throughout the comparisons.

Despite the limitations, there are numerous strengths of this study to highlight. First, the considerable size of our cohorts minimizes many of the limitations of using aggregate data. Second, by using EHR-derived data, we were able to assess the utilization of medications with more detail than other traditional insurance-based datasets. Relatedly, the validity of the MHD outcome results are supported by similar and concomitant increases in medication usage to treat these conditions. Fourth, the EHR data also allowed us to identify strictly oral opioids and benzodiazepines, thereby avoiding any confounding of medications administered while hospitalized, as well as those administered for sedation during medical procedures.

In conclusion, compared with controls, patients with AP are significantly more likely to develop a new-onset MHD, and receive psychiatric medication for that MHD, within one year. Patients with more severe disease (i.e. ANP) are at an even higher risk for MHDs compared with patients without necrosis. These results suggest that for some, the established risk of developing a MHD in association with CP may in fact occur prior to the onset of overt CP. Large prospective studies with long-term follow-up are required to support this observation.

Guarantor of article

Zachary L. Smith, DO.

Author roles

Conception & Design: ZLS.
Data collection: ZLS.
Aggregate data assembly: ZLS, OS.
Analysis and interpretation of the data: ZLS.
Drafting the article: KK, OS and ZLS.
Critical revision of the article for important intellectual content: all authors.
Manuscript revision/final approval: all authors.

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Declaration of competing interest

None of the authors disclose relevant conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2023.01.008.

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