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Readmission of patients with hypertriglyceridemia-induced acute pancreatitis: a prospective cohort study

Yuxiang Liu[1†], Ling Ding[1†], Xin Xu[1], Langyi Guan[1], Wenhua He[1], Liang Xia[1], Nonghua Lu[1] and Yin Zhu[1*]

Abstract

Background Acute pancreatitis (AP) is a common cause of acute hospital admissions in digestive system diseases. In East Asia, hypertriglyceridemia is gradually emerged as the second most common cause of pancreatitis. Vigilance for recurrence and unplanned readmissions due to other causes is still necessary after discharge. studies on hypertriglyceridemia-induced acute pancreatitis (HTG-AP) are scarce and mainly consists of retrospective studies.

Methods This was a prospective cohort study of adult patients with first episode of HTG-AP from December 2019 to February 2021 who were followed up for two years. Unscheduled readmission after the index discharge was the primary outcome. The Cox proportional-hazards model, and the Fine and Gray's competing-risk model were applied to the analyses.

Results Totally, 293 survival patients were followed-up after discharge. The overall unplanned readmission rate was 30.0% in two years. Among them, 60 (20.5%) patients were readmitted to hospital once, 16 (5.5%) were readmitted twice, and 13 (4.4%) were readmitted three times or more. In summary, a total of 143 cases of readmission information were collected during the follow-up period. The recurrence accounts for a significant 77.3% proportion and stands as the primary cause for readmission. Cox regression model favors infection (Hazard ratio [HR], 3.066; 95% confidence interval [CI], 1.192–7.888; $P=0.02$) and age lower than 41.5 years old (HR, 3.157; 95% CI 1.883–5.292; $P<0.01$) as independent risk factors for patient readmission by multivariate analysis. The competing-risk model support the similar results compared with the former.

Conclusion Unplanned readmission of patients with hypertriglyceridemia-induced acute pancreatitis is common, especially for young patients with occurrence of any infection during hospitalization, and warrant further investigation.

Keywords Readmissions, Hypertriglyceridemia-induced acute pancreatitis, Recurrence

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Introduction

Hypertriglyceridemia (HTG) is the third leading cause of acute pancreatitis (AP), and the weighted mean prevalence of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is 9% [1]. Compared to other etiologies, patients with HTG-AP had a higher risk of developing severe AP [2]. In China, this proportion is greater than that in other regions, potentially reaching 14-26% [3, 4, 5]. Readmission after discharge is a major problem after the initial episode of AP, and the readmission rate varies among patients with different etiologies and from different institutions.

A large sample database analysis concluded that the readmission rate for all-cause pancreatitis was 16.2% [6]. A meta-analysis pointed out the readmission rate for biliary, alcoholic and hypertriglyceridemia was 4–37%, 2–60% and 0–5% [7]. Currently, readmissions for AP are discussed mainly for biliary and alcoholic etiology, and studies on readmissions for HTG-AP are scarce [8, 9, 10]. Hypertriglyceridemia, can precipitate readmission and increase the risk of recurrent AP, especially in recurrent AP [9]. Another study considered 13.5% as the readmission rate for HTG-AP in 30 days [8].The incidence of HTG-AP in East Asia is steadily increasing [11], yet corresponding readmission studies in East Asia are relative limited. Also, mostly retrospective study, shorter time spans limit them not capable to derive consistent clinical guidance.

Long-term follow-up after discharge from pancreatitis post-discharge mortality received profound insight [12], with limited research on readmissions specific to etiology. To further understand the extent to which patients were readmitted after discharge, we conducted a two-year follow-up period for a prospective study to investigate the incidence, clinical features, and independent risk factors for readmission of patients with HTG-AP.

Method

Study design and participants

This was a single-center, prospective, observational cohort study, guided by STROBE Statement. Following to the prior study, a total of 293 patients diagnosed with HTG-AP for the first time and admitted to our tertiary care referral center in China between December 2019 and February 2021 were enrolled [13]. The diagnosis of AP requires two of the following three criteria: (1) upper abdominal pain, (2) serum lipase or amylase activity at least three times greater than the upper limit of normal, and (3) characteristic findings of AP on imaging [14]. HTG-AP was diagnosed when patients had AP with a serum TG concentration > 1000 mg/dL (11.3 mmol/L) or a serum TG concentration of 500–1000 mg/dL (5.65–11.3 mmol/L) accompanied by chylous serum with the absence of other etiologies for AP [15]. Patients with AP etiologies other than HTG were excluded, as were those with comorbidities of chronic pancreatitis and pancreatic neoplasm. Patients who died during hospitalization were also excluded. This single-center observational follow-up cohort study is based on a prior study approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (Approval No. 2019122). This observational cohort study utilizes the same ethically approved dataset but shifts the focus to hospital readmission patterns. The study was performed in accordance with the Declaration of Helsinki principles. All participants provided written informed consent for the use of their data in subsequent research.

Data collection and definition

The primary outcome was unplanned readmission of patients with HTG-AP, which was defined as readmission to a hospital or health care facility for medical treatment after being discharged from a previous hospitalization. Those patients planned readmission due to pregnancy, cholecystectomy, drainage tube or enteral nutrition tube removal, stent change or removal were considered as non-readmission. Moreover, the exact reason and time for readmission were also collected. All participants provided written informed consent.

The risk factors collected included demographic characteristics, local and systematic complications, medical interventions and other common clinical profiles during index hospitalization. The demographic characteristics included sex, age at diagnosis, history of hypertension, diabetes, smoking and alcohol. Local complications included acute peripancreatic fluid collection, acute necrotic collection, pancreatic pseudocysts, and walled-off necrosis. Other laboratory results included infection, thrombosis, pleural effusion, abdominal ascites, cardiac effusion and abdominal compartment syndrome. Infection refers to the presence of any bacterium in patient specimens, including blood, sputum, necrotic tissue and any other laboratory specimens 48 h after hospitalization. Clinical therapy was defined as drainage tube placement, invasive ventilation, oral lipid-lowering medication, hemofiltration, heparin and insulin usage. The data were collected by trained clinical research administrators. The patients were followed up twice at the end of every year according to their discharge time.

The data sources included direct communications, telephone consultations, and electronic medical records. All the patients required an annual follow-up after their first discharge. Follow-up focused on the presence of unplanned readmissions, the number of readmissions, the timing, and the etiology of this episode. Several methods have been applied to obtain credible results. Communicating via WeChat, phone calls, and direct searches in medical archives were the most commonly

used methods for obtaining results. Patients for whom no information could be obtained through any of the three methods were classified as lost to follow-up.

Statistical analyses

Quantitative variables are presented as medians (interquartile ranges, IQRs). The ROC curves were created to obtain cutoff values based on the age and readmissions. The AUC curve and Youden index was calculated using SPSS software, with the corresponding value at the maximum point being identified as the optimal cut-off value. All the exposure factors were screened by multiple linear regression (variance inflation factor > 5 equals collinearity) and included in the lateral analysis. The Kaplan–Meier survival curve was utilized to compute the probability of remaining free from pancreatitis over a two-year period. All variables were subjected to univariable analysis, and the risk factors identified in the univariate analysis ($P < 0.1$) were subsequently applied in the multivariate analysis to determine the independent risk factors. In the competing-risk model, tested with Gray's test, the readmission rate was calculated using the cumulative incidence function and was ultimately plotted using the Nelson–Aalen estimator curve. The screened risk factors were placed in Fine and Gray's competing-risk model to identify the independent risk factors. The hazard ratio (HR) and 95% confidence interval (CI) were estimated with the Cox model, and the subdistribution hazard ratio (SHR) and 95% confidence interval (CI) were estimated with the competing-risk model. Two-tailed P values < 0.05 were considered to indicate statistical significance. IBM SPSS Statistics 27 was used for Cox modeling and multiple linear regression analysis. RStudio in R4.3.2 was used for competing risk modeling.

Results

Characteristics of unplanned readmission

After excluding patients died during hospitalization, a total of 293 patients were enrolled in this prospective observational study, as shown in Fig. 1. Tables 1 and 2 present the Clinical and demographic characteristics of the study population. Eighteen (6.1%) were lost to follow-up during the two-year period. Among all the patients, the median age at admission was 40.0 years (32–46), with a male predominance (229, 78.2%). Hypertension and diabetes mellitus were documented in 8 (2.7%) and 55 (18.8%) patients, respectively. The majority of patients were diagnosed with moderately severe acute pancreatitis (159, 54.3%), while the majority were found to have edematous pancreatitis (198, 67.6%). The overall readmission rate was 30.0% ($n = 88$), and the first 12-month and second 12-month readmission rates were 18.1% and 15.7%, respectively. The median number of readmissions for each readmitted patient was 1.56 [1, 2], and a total of 143 readmissions were observed. In terms of quantity and frequency, 60 (20.5%) patients experienced one readmission within a two-year period, while 16 (5.5%) patients had two readmissions within the same timeframe. Twelve (4%) patients exhibited a higher frequency of readmission. In terms of etiology, 77.3% of patients were readmitted for disease recurrence, with hypertriglyceridemia accounting for 66% of these cases. Additionally, 12.8% of recurrences were attributed to biliary issues, while none were related to alcohol. The remaining cases may be idiopathic.14.7% were readmitted for fewer instances of abdominal pain, and 2.4% were readmitted for treating local pancreatitis complications. Although no patients were diagnosed with pancreatogenic diabetes during hospitalization, 1.7% of them, who had pre-existing diabetes, were readmitted for better blood glucose control after discharge. Two patients died due to multiple-organ failure induced by acute severe pancreatitis complicated with septicemia. All the patients were discharged with fenofibrate, but the lateral administration was censored. We collected cultures from blood and pancreatic open necrosectomy. The results suggested that Acinetobacter baumannii and Klebsiella pneumoniae were common infectious organisms in blood cultures, whereas Candida smoothii was common in puncture cultures.

According to the follow-up, readmitted patients tend to be younger overall, with a higher proportion of males than females. Among readmitted patients, those previously diagnosed with severe pancreatitis have a higher proportion, while the opposite is observed for patients with moderately severe pancreatitis. The detailed baseline characteristics, clinical profiles at discharge and clinical outcomes at the index hospitalization are depicted in Table 3. The probability of readmission for patients with infections during hospitalization (11.12.5%) was significantly greater than that for patients without infections (6.2.9%) ($p = 0.01$). There was a significantly greater incidence of abdominal ascites in the readmitted patients (40, 45.5%) than in the other patients (67, 32.7%) ($p = 0.037$). ICU admittance was significantly greater in the readmitted group (29,33.0%) than in the non-readmitted group (42,20.5%, $p = 0.022$).

Risk factors for HTG-AP readmission

To avoid collinearity issues, we employed multiple linear regression for the lateral analysis, with the results shown in Stable (1) In sFig 1, age was analyzed as the continuous variable, with the occurrence of unplanned readmission serving as the binary outcome variable. ROC curves were constructed, yielding an AUC of 0.624 (95% CI: [0.559,0.689]). The AUC value was further quantified, and the corresponding optimal cut-off value was determined to be 41.5 years old. Prognostic factors associated with unplanned readmissions for COX models are presented

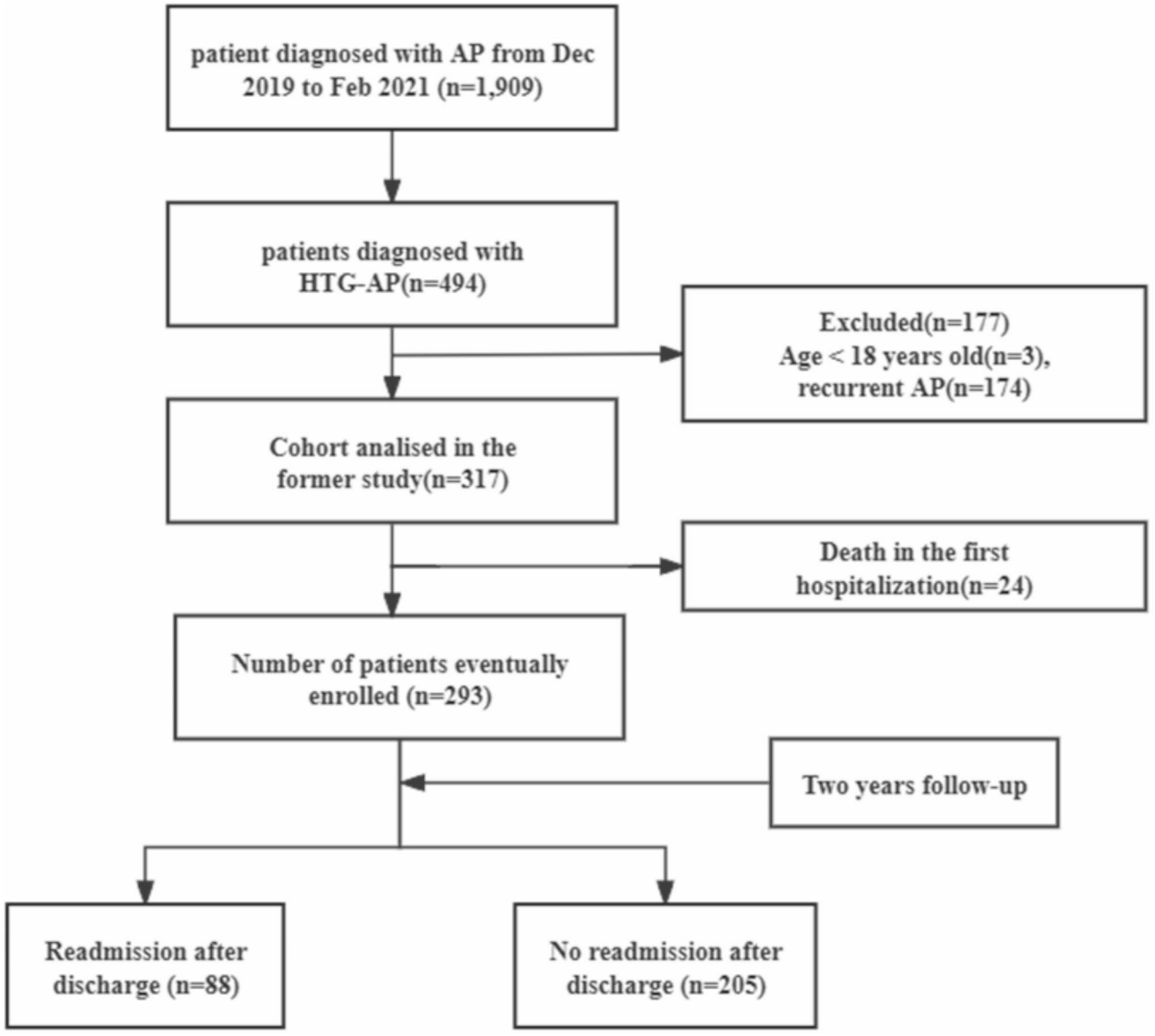

Fig. 1 Enrollment of the post-hoc analysis

Table 1 Demographic characteristics of the study cohort

	All patients (*n* = 293)
Sex(male)	229(78.2%)
Age at diagnosis, years	**40.0(32,46)**
Body mass index, kg/m2	**26.3(24.0,28.5)**
History of hypertension	**8(2.7%)**
History of diabetes	**55(18.8%)**
History of smoking	**122(41.6%)**
History of alcohol intake	**70(23.9%)**

in STable (2) The following factors were found to significantly prognosticate readmission: abdominal ascites ($p = 0.013$), infection ($p < 0.01$), drainage-tube ($p = 0.01$), renal failure ($p = 0.054$), circulatory failure ($p = 0.079$), ICU attendance ($p = 0.007$), hemofiltration ($p = 0.076$) and age stratification ($p < 0.01$). According to our multivariate analysis in Stable 4, only infection (HR = 3.066, 95% CI = 1.192–7.888, $P = 0.020$) and age younger than 41.5 years (HR = 3.157, 95% CI = 1.883–5.292, $P < 0.001$) were found to be independent risk factors. Subsequently, Kaplan–Meier curves were generated to plot the cumulative readmission-free rate at two years, as shown in Fig. 2. The results of the univariate analysis and multivariate analysis also confirmed these findings from Cox regression model, with only infection (SHR = 3.064, 95% CI = 1.161–8.090, $P = 0.024$) and age younger than 41.5 years (SHR = 3.154, 95% CI = 1.861–5.345, $P < 0.001$) identified as independent risk factors for readmission, which presented in Stable 3 and Stable 5.

Table 2 Clinical characteristics of the study cohort.all patients($n=293$)

	All patients ($n=293$)
Severity of AP	
Mild AP	**71(24.2%)**
Moderately severe AP	**159(54.3%)**
Severe AP	**63(21.5%)**
Type of AP	
Interstitial edematous pancreatitis	**198(67.6%)**
Necrotizing pancreatitis	**95(32.4%)**
Local complications	
None	**94(32.1%)**
Acute peripancreatic fluid collection	**103(35.2%)**
Acute necrotic collection	**79(27.0%)**
Pancreatic pseudocyst	**1(0.3%)**
Walled-off necrosis	**16(5.5%)**
Other laboratory results	
Infection	**17(5.8%)**
Thrombosis	**6(2.05%)**
Pleural effusion	**251(85.7%)**
Abdominal ascites	**107(36.5%)**
Cardiac effusion	**12(4.1%)**
Abdominal compartment syndrome	**5(1.7%)**
Clinical therapy	
Drainage-tube	**16(5.5%)**
Nasojejunal feeding tube	**92(31.4%)**
Invasive ventilation	**13(4.4%)**
Hemofiltration	**12(4.1%)**
Heparin usage	**189(64.5%)**
Insulin usage	**239(81.6%)**
Length of hospital stay	**13.07(6,1%)**
Intensive unit care stay	**71(24.0%)**
Hospital costs, ×103CNY	**49.2(12.1,46.9)**

Discussion

Currently, studies on readmission for HTG-AP is predominantly limited to retrospective studies, with relatively short follow-up periods. After retrospectively analyzed a nationwide database. While the study has a large sample size, it falls under the category of a retrospective study [8]. Therefore, we utilized data from a prospective study and conducted a two-year follow-up to further investigate the risk factors for unplanned readmission in HTG-AP. According to our follow-up data, the 12-month and 24-month readmission rates were 18.1% and 30.0%, respectively.

Studies primarily focus on unplanned readmissions for overall, biliary, and alcoholic pancreatitis, with limited data on HTG-AP unplanned readmissions [8]. Kichloo et al., based on a retrospective study, emphasized hypertension, protein-energy malnutrition, Charlson Comorbidity Index (CCI) scores ≥ 3, chronic kidney disease, and discharge against medical advice as independent risk factors for 30-day readmission in HTG-AP patients [8]. Wehbe et al., in a retrospective study, failed to identify independent risk factors for readmission in necrotizing pancreatitis [16]. Kumar et al. highlighted the impact of self-discharge and higher CCI on readmission [17]. Our study underscores the influence of post-admission infections (such as sepsis or infected pancreatic necrosis) and age less than 42 years on unplanned readmissions after patient discharge. Given that our research utilizes data from our center in a multicenter prospective study, the evidence quality is higher.

A seven-year study conducted at a tertiary center in Romania highlighted that patients with HTG-AP were younger compared to those with other types of pancreatitis [18]. The study also identified a 31% recurrence rate among these patients. Recurrence is the most common reason for readmission in pancreatitis cases. Consequently, patients with HTG-AP are more likely to experience unplanned readmissions than those with other forms of pancreatitis. Our findings is in congruence with that study and indicates infection and age less than 42 years being independent risk factors for unplanned readmission in HTG-AP patients. The propensity for younger patients to develop and experience recurrent HTG-AP may be attributed to poor dietary habits and lower adherence to treatment regimens. Among patients with infections during hospitalization, the majority are diagnosed with severe pancreatitis, potentially leading to an increased risk of unplanned readmissions. Previous research has suggested that readmission risk decreased with increasing age [19] and being under 60 years old is an independent risk factor for AP recurrence [20]. Surprisingly, after incorporating organ failure parameters into the analysis, we found no clear association between respiratory/circulatory failure and unplanned readmissions. Further scrutiny revealed two potential explanations. First, rare occurrence of circulatory failure likely introduced random variability, limiting detection of true associations. transient respiratory failure could have reduced its clinical representativeness, potentially diminishing their prognostic relevance for longer-term outcomes like readmissions. Second, although organ failure is strongly associated with the severity of AP, our analysis revealed no statistically significant link between the severity of pancreatitis and unplanned readmissions. Our study further indicated its impact on unplanned readmissions. We found that the etiology of AP recurrence after discharge from HTG-AP was not exclusively hypertriglyceridemia, and a considerable number of patients were readmitted for biliary pancreatitis or idiopathic pancreatitis.

Studies on pancreatitis readmission have reported that all-cause readmission rates can range from 19–34% [20, 21], with some reaching as high as 72% in patients with necrotic pancreatitis [22]. Our study suggested that patients with HTG-AP also have a high probability of

Table 3 Clinical profile of the patients discharged from our center

	Readmission	No readmission	*P* value
Demographic characteristics			
Sex(male)	72(81.8%)	157(76.6%)	0.132
Sex(female)	16(18.2%)	48(23.4%)	
History of hypertension(yes)	3(3.4%)	5(2.4%)	0.640
Hypertension(no)	85(96.6%)	200(97.6%)	
History of diabetes(yes)	19(21.6%)	34(16.6%)	0.308
History of diabetes(no)	69(78.4%)	171(83.4%)	
Severity of AP			
Mild AP	22(25.0%)	49(23.9%)	0.375
Moderately severe AP	43(48.9%)	116(56.6%)	
Severe AP	23(26.1%)	40(19.5%)	
Type of AP			
Interstitial edematous pancreatitis	56(63.6%)	142(69.3%)	0.345
Necrotizing pancreatitis	32(36.4%)	63(30.7%)	
Local complications			
None	29(33.0%)	65(31.7%)	0.068
Acute peripancreatic fluid collection	26(29.5%)	77(37.5%)	
Acute necrotic collection	23(26.1%)	56(27.3%)	
Pancreatic pseudocyst	1(1.1%)	0(0%)	
Walled-off necrosis	9(10.2%)	7(3.4%)	
Other laboratory findings			
Infections(yes)	11(12.5%)	6(2.9%)	0.001
Infections(no)	77(87.5%)	199(97.1%)	
Thrombosis(yes)	3(3.4%)	3(1.5%)	0.281
Thrombosis(no)	85(96.6%)	202(98.5%)	
Pleural effusion(yes)	49(55.7%)	114(55.6%)	0.991
Pleural effusion(no)	39(44.3%)	91(44.4%)	
Abdominal ascites(yes)	40(45.5%)	67(32.7%)	0.037
Abdominal ascites(no)	48(55.5%)	138(67.3%)	
Cardiac effusion(yes)	1(1.1%)	11(5.4%)	0.094
Cardiac effusion(no)	87(98.9%)	194(94.6%)	
Abdominal compartment syndrome(yes)	2(2.3%)	3(1.5%)	0.624
Abdominal compartment syndrome(no)	8(97.7%)	202(98.5%)	
Renal failure(yes)	9(10.2%)	10(4.9%)	0.088
Renal failure(no)	79(89.8%)	195(95.1%)	
Respiratory failure(yes)	38(43.2%)	82(40.0%)	0.258
Respiratory failure(no)	50(56.8%)	123(60.0%)	
Circulatory failure(yes)	8(9.1%)	9(4.4%)	0.115
Circulatory failure(no)	80(90.9%)	196(95.6%)	
Clinical therapy			
Drainage-tube(yes)	10(11.4%)	6(2.9%)	0.004
Drainage-tube(no)	78(88.6%)	199(97.1%)	
Invasive ventilation(yes)	6(6.8%)	7(3.4%)	0.195
Invasive ventilation(no)	82(93.2%)	198(96.6%)	
Hemofiltration(yes)	6(6.8%)	6(2.9%)	0.123
Hemofiltration(no)	82(93.2%)	199(97.1%)	
Intensive unit care(yes)	29(33.0%)	42(20.5%)	0.022
Intensive unit care(no)	59(67.0%)	163(79.5%)	

readmission after discharge, as the overall readmission rate can reach 30.0%. A high HTG-AP readmission rate suggests the necessity for regular postdischarge follow-up and close monitoring.

There are also several limitations in this study. First, there are reports suggesting that protein energy malnutrition is a potential risk factor for HTG-AP readmission [8], but such results are difficult to collect, and disparities

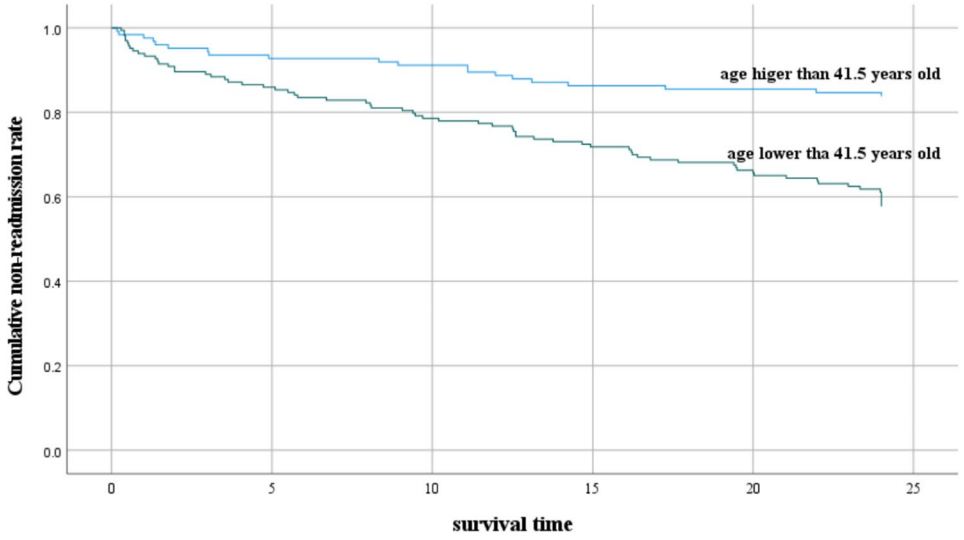

Fig. 2 The cumulative non-readmission curve by Kaplan-Meier curve

in economic conditions can also result in variations in postdischarge nutritional support, therefore, we lack relevant nutritional information. Besides, all patients were discharged with fenofibrate, but the duration and frequency of medication usage after discharge were not obtained, which may impact readmission for AP. Additionally, the follow-up data collected in this study were from patients in a single center, which may introduce limitations to the generalizability of the findings. The universality of the results could be compromised by this constraint.

Conclusion

The readmission rate for patients with HTG-AP can reach 30.0% within 24 months after discharge. Early readmissions due to local complications are quite common, and the risk of AP recurrence increases with the duration of follow-up. Therefore, to reduce readmissions in this vulnerable population, close follow-up and frequent communication are necessary.

Abbreviations

HTG-AP	hypertriglyceridemia-induced acute pancreatitis
AP	acute pancreatitis
HTG	hypertriglyceridemia
IQRs	interquartile ranges
HR	hazard ratio
CI	confidence interval
SHR	subdistribution hazard ratio
CNY	Chinese yuan
CCI	Charlson Comorbidity Index

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Author contributions

Yuxiang Liu: Conceptualization, Methodology, Formal analysis, Writing–original draft. Ling Ding: Conceptualization, Methodology, Investigation, Data curation. Xin Xu: Investigation, Data curation. Langyi Guan: Investigation, Data curation. Wenhua He: review & editing. Liang Xia: review & editing. Nonghua Lu: Conceptualization, Project administration. Yin Zhu: Conceptualization, Project administration, Funding acquisition. All authors approved the final version of the manuscript.

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Data availability

The data supporting the findings of this study are available in the supplementary material of this article or from the corresponding author upon reasonable request.

Declarations

Ethics declarations

The consent got approved by institutional review boards of the First Affiliated Hospital of Nanchang University (No. 2,019,122). Written informed consent was obtained from all participants, and all methods were performed in accordance with guidelines of the Declaration of Helsinki of the World Medical Association.

Consent for publication

Not applicable..

Competing interests

The authors declare no competing interests.

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