https://doi.org/10.34883/PI.2022.11.1.001
UDC 616.37-002.1-036:616-022.7]-085

Dronov O.✉, Kovalska I., Gorlach A., Kozachuk Ye., Shchyhel I., Ivanets T.
Bogomolets National Medical University, Kyiv, Ukraine

Extrapancreatic Infection is a Factor in the Unfavorable Course of Acute Severe Infected Pancreatitis

Conflict of interest: nothing to declare.
Authors' contribution: Dronov O., Kovalskaya I. – concept and design of the study, editing; Gorlach A., Kozachuk Ye. – the collection of material, processing, writing the text; Schyhel I., Ivanets T. – processing materials, data analysis, evaluation of research results.
The article is published in the author's edition.

Submitted: 18.02.2022
Accepted: 28.02.2022
Contacts: general.surg1@nmu.ua

Abstract

Purpose. To evaluate the impact of extrapancreatic infection on the course and results of acute severe infected pancreatitis treatment.
Materials. In this study, 63 patients were included: group I (n=38) – patients with pancreatic and extrapancreatic infection; group II (n=25) – patients with pancreatic infection only
Results. 189 microbial isolates were obtained, which were represented by 12 strains of bacteria. The development of pancreatic infection was associated with contamination by Escherichia coli (26.7%), Enterococcus feacium (20.0%), Staphylococcus aureus (16.7%), Klebsiella pneumoniae (18.8%), and 15.6% Enterobacter species), which were subsequently replaced by Klebsiella pneumoniae (23.0% and 24.2%), Acinetobacter baumannii (19.6% and 18.2%) and Pseudomonas aeruginosa (16.0% and 18.2%). The dynamics of antibiotic resistance development were characterized by a time-dependent increase in the frequency of extensive and panresistant microflora. The main localizations of EPI were bile (Escherichia coli, Klebsiella pneumoniae), respiratory system (Pseudomonas aeruginosa and Acinetobacter baumannii) and blood (Staphylococcus aureus and Staphylococcus saprophyticus). The presence of extrapancreatic infection increased the probability of extensive – resistant bacterial strains by 2.5 times (R^2=0.61; p=0.019). The development of extrapancreatic infection contributed to a significant increase in the severity of multiple organ failure, prolonged of stay in the ICU and increase the incidence of hospital mortality after 14 days.
Conclusion. The presence of EPI foci in patients with severe acute infected necrotic pancreatitis negatively affects the effectiveness of antibiotic therapy and contributes to the appearance of extensive drug-resistant strains of microorganisms. Extrapancreatic infection worsens the clinical course of SAP complicated by PI and increases the risk of in-hospital mortality rate by 10 times.
Keywords: severe acute pancreatitis, pancreatic infection, extrapancreatic infection, antidrug resistance, pancreatitis treatment

Дронов А.И.✉, Ковальськая И.А., Горлач А.И., Козачук Е.С., Щигель И.А., Иванец Т.Ю.
Национальный медицинский университет имени А.А. Богомольца, Киев, Украина

Экстрапанкреатическая инфекция как фактор неблагоприятного течения острого тяжелого инфицированного панкреатита

Конфликт интересов: не заявлен.
Вклад авторов: Дронов А.И., Ковальская И.А. – концепция и дизайн исследования, редактирование; Горлач А.И., Козачук Е.С. – сбор материала, обработка, написание текста; Щигель И.А., Иванец Т.Ю. – обработка материалов, анализ данных, оценка результатов исследования.
Статья опубликована в авторской редакции.

Подана: 18.02.2022
Принята: 28.02.2022
Контакты: general.surg1@nmu.ua

Резюме

Цель. Оценить влияние экстрапанкреатической инфекции (ЭПИ) на течение и результаты лечения острого тяжелого инфицированного панкреатита.
Материалы. В исследование включено 63 пациента: I группа (n=38) – пациенты с панкреатической и экстрапанкреатической инфекцией; II группа (n=25) – пациенты только с панкреатической инфекцией.
Результаты. Получено 189 микробных изолятов, которые были представлены 12 штаммами бактерий. Развитие панкреатической инфекции было связано с контаминацией Escherichia coli (26,7%), Enterococcus feacium (20,0%), Staphylococcus aureus (16,7%), Klebsiella pneumoniae (18,8%) и Enterobacter (15,6%), которые впоследствии были заменены Klebsiella pneumoniae (23,0% и 24,2%), Acinetobacter baumannii (19,6% и 18,2%) и Pseudomonas aeruginosa (16,0% и 18,2%). Динамика развития антибиотикорезистентности характеризовалась увеличением во времени частоты экстенсивной и панрезистентной микрофлоры. Основными локализациями ЭПИ были желчь (Escherichia coli, Klebsiella pneumoniae), дыхательная система (Pseudomonas aeruginosa и Acinetobacter baumannii) и кровь (Staphylococcus aureus и Staphylococcus saprophyticus). Наличие экстрапанкреатической инфекции повышало вероятность экстенсивно-резистентных штаммов бактерий в 2,5 раза (R2=0,61; p=0,019). Развитие экстрапанкреатической инфекции способствовало значительному нарастанию тяжести полиорганной недостаточности, увеличению продолжительности пребывания в ОРИТ и увеличению частоты госпитальной летальности через 14 дней.
Заключение. Наличие очагов ЭПИ у пациентов с тяжелым течением острого инфицированного некротического панкреатита негативно влияет на эффективность антибактериальной терапии и способствует появлению полирезистентных штаммов микроорганизмов. Экстрапанкреатическая инфекция усугубляет клиническую причину острого тяжелого инфицированного панкреатита и увеличивает риск госпитальной летальности в 10 раз.
Ключевые слова: тяжелый острый панкреатит, панкреатическая инфекция, экстрапанкреатическая инфекция, антибиотикорезистентность, лечение панкреатита

INTRODUCTION

Acute pancreatitis (AP) takes third place in the frequency of hospitalizations and is the leading cause of death in patients with acute surgical pathology of the gastrointestinal tract. The overall mortality in AP is 2–9% and can reach 20–30% in severe acute pancreatitis (SAP) [1, 2].

Despite improved diagnostic and treatment modalities, the higher rate of hospital mortality due to SAP has remained unchanged over the last decade. Therefore, the study of unfavorable factors that directly affect the clinical course and prognosis of patients with SAP plays a special role in its reduction [4].

The persistent of multiorgan failure and pancreatic infection (PI) development, which is present in almost 20–40% of cases, is the leading cause for unsatisfactory results of patients with SAP treatment [2, 3].

To date, researchers have focused their attention on studying PI. However, recently the role of extrapancreatic infection as a prognostic factor for unsatisfactory outcomes of SAP treatment has been actively investigated [4, 5].

Extrapancreatic infection (EPI) is an infection that is localized in organs and tissues outside the pancreas and peripancreatic tissue, documented during hospital stay [6]. The most common localization of EPI is blood, respiratory tract, urinary tract, abdominal cavity, biliary tract [2, 4].

According to a few studies, the development of EPI contributes to the deterioration of the clinical course of GTP and may increase the incidence of hospital mortality rate. However, the number of studies remains insufficient [1, 2, 4, 7, 8].

PURPOSE OF THE STUDY

To evaluate the impact of extrapancreatic infection on the course and results of acute severe infected pancreatitis treatment.

MATERIALS AND METHODS

The study design is a single-center cohort retrospective study.

We analyzed 71 case histories of patients with acute severe infected pancreatitis who were treated at the clinical base of the Department of General Surgery №1 Bogomolets National Medical University in the period from 2019 to 2020.

The inclusion criteria were patients with severe acute pancreatitis complicated by pancreatic infection (PI), the possibility of bacteriological monitoring of pancreatic infection (PI) in the control terms.

The diagnosis of SAP and the severity of pancreatic lesions assessment made according to the Atlanta 2012 classification criteria, BISAP (The Bedside Index for Severity in Acute Pancreatitis), Moderated Marshall score, MCTSI (Modified CT Severity Index), and CT necrosis index [9–12].

The sources of pancreatic infection were acute pancreatic necrosis and acute fluid peripancreatic collections with proven positive bacteriological cultures.

Bacteriological monitoring of pancreatic infection (PI) performed in two stages: Stage I (initial) – primary identification of the pathogen PI, for 8–14 days; Stage II (final) – completion of inpatient treatment, 48–60 days of illness.

The criterion for non-inclusion in the study was the lack of bacteriologically proven PI.

The exclusion criteria were the impossibility of bacteriological monitoring of PI and failed diagnostic compliance. Eight of 71 patients with PI were excluded from the study (5 of them died in the first 14 days of the disease, 3 patients did not comply with the study).

Thus, 63 patients were included in the study and divided, according to bacteriologically verified extrapancreatic infection presence, into two groups: group I (n=38) – patients with pancreatic and extrapancreatic infection; group II (n=25) – patients with pancreatic infection only.

Extrapancreatic infection is defined as foci of infection with localization in organs and tissues out of pancreatic and peripancreatic tissue – biliary, respiratory, catheter-associated infection, urinary tract infection, bacteremia [6].

Microbiological identification of the pathogen EPI was performed before the initial identification of the pathogen PI and between the I and II stages of the study [5]. The main indication for bacteriological culturing of samples from extrapancreatic sources of infection was the presence of clinical symptoms by the location of the foci.

General characteristics of patients, etiology, and severity of pancreatic lesions in the study groups are presented in table 1.

The study groups did not differ by age (p=0.06), the severity of GP according to BISAP (p=0.37), Modified Marshall score (p=0.19), the degree of pancreatic lesions according to MCTSI (p=0.1) and CT index of necrosis (p=0.1). However, there was a statistically significant difference by gender (χ^2=7.17, p=0.007) and the etiology of GTP (χ^2=41.07, p<0.001). In particular, the group I was dominated by women and pancreatitis of biliary etiology, and group II – men and alcoholic pancreatitis.

Primary endpoints:

1. Structure of pancreatic and extrapancreatic infection pathogens.
2. The level of acquired antibiotic resistance (ADR) of microorganisms.
3. Dynamics of the infectious process.
4. Mortality after 14 days.

Table 1
General characteristics of patients, etiology, and severity of pancreatic lesions in the study groups

Characteristics		**Group I (n=38)**	**Group II (n=25)**	**P-value**
Age*, years		54 (42–60)	49 (40–59)	0.06
Gender, n (%)	Male	13 (34.3)	18 (72)	0.007
	Female	25 (65.7)	7 (28)	
Etiology, n (%)	Alcoholic	7(18.4)	21 (84)	<0.001
	Biliary	26 (68.5)	–	
	Hypertriglyceride	–	4 (16)	
	Postoperative	5 (13.1)	–	
BISAP*, scores		3 (3–4)	3 (3–4)	0.37
Modefied Marshall score*, scores		7 (6–8)	6.5 (6–8)	0.19
MCTSI*, scores		8 (8–10)	8 (8–8)	0.1
CT index of necrosis *, points		2 (2–4)	4 (2–4)	0.1

Notes: * Median (25%–75% of the quartile) – Me (QI–QIII): BISAP – The Bedside Index for Severity in Acute Pancreatitis; Modified Marshall score – the severity scores for acute pancreatitis; MCTSI – Modified CT Severity Index.

Secondary study endpoints were:

1. Period of stay in the ICU.
2. Period of hospital stay.

Biological samples from PI foci were analyzed in all patients (aspirate of acute peripancreatic fluid collections, necrotic discharges from the omental sac and retroperitoneal space drains), and in group II – in addition from foci of EPI (sputum, pleural fluid, urine, bile, intravenous catheters).

The obtained biological samples were examined microscopically with Gram staining. Bacteriological culturing was performed to obtain isolated strains. Sensitivity to antibiotics was assessed using the disco-diffusion method. The total bacteria count ≥105 CFU/ml was considered etiologically significant. Aerobic and facultative anaerobic flora were studied. The identification of obligate anaerobes was not performed.

The level of acquired ABR microorganisms in patients of both groups was determined according to the recommendations of ECDC (European Center for Disease Prevention Control, 2012): AMR "–", MDR, XDR, PDR [13].

The dynamics of the infectious process were assessed by the SOFA scale (The Sepsis-related Organ Failure Assessment), namely the delta SOFA indicator – the difference between the maximum level of SOFA in the late phase of the disease and the SOFA level at the initial diagnosis of infected necrotic pancreatitis [14].

The cause of the disease was assessed from the time of hospitalization to the clinical outcome of treatment (discharge with improvement or death). The observation period averaged 42.2±13.7 days.

Statistical analysis of the data was performed using SPSS 22.0 software for Windows. The following methods of statistical analysis were used: descriptive statistics, comparison of mean values using Student's T-test (for variables that are expressed in the scale of relations and have the correct distribution), and Mann – Whitney U-test; Particle comparisons were performed using Pearson's chi 2 for independent samples and MacNemar for dichotomous variables in related samples. Phi and V Crammer's criteria were used for correlation analysis. The significance of differences in cumulative frequencies was determined using binary logistic regression. The null hypothesis (no differences between variables) was rejected at $p<0.05$.

■ RESULTS

In the studied patients, 189 microbial isolates were obtained, which were represented by 12 strains of bacteria. Gram-positive microorganisms were identified in 55 cases (29.1%), gram-negative in 134 cases (70.9%). Mix infection was observed in 80 cases (42.3%) and was represented by a combination of 2 and 3 microorganisms; mono-infection in 109 cases (57.7%). In group I (n=38), 91 microbial isolates from PI and 34 isolates from EPI were obtained. In group II (n=25), 98 microbial isolates were cultured during bacteriological monitoring of PI foci.

At the first stage of PI verification in the first group, Escherichia coli (26.7%), Enterococcus feacium (20.0%), and Staphylococcus aureus (16.7%) were mainly sown. The Escherichia coli (34.3%), Klebsiella pneumoniae (18.8%), and Enterobacter species (15.6%) were dominated in the second group.

Subsequent bacteriological monitoring showed changes in the structure of the PI microflora. In particular, Klebsiella pneumoniae (23.0% and 24.2%), Acinetobacter

baumannii (19.6% and 18.2%) and Pseudomonas aeruginosa (16.0% and 18.2%) were the most common microbial isolates in both groups.

At the first stage of bacteriological culturing in the group of patients with EPI, multi- and extensive drug-resistant microorganisms prevailed among antibiotic-resistant microorganisms – 13.3% and 6.6%, respectively, and in the group without EPI – only multidrug-resistant cultures (15.6%).

There was no statistically significant difference in the frequency of antibiotic resistance of microorganisms at the first stage in the study groups (p=0.195). However, at the second stage, a statistically significant difference in antibiotic resistance was found between the study groups (χ^2=5.67, p=0.019), which increased towards the frequency of detection of multidrug-resistant (26.2% and 42.4%, respectively; p=0.055) and extensive drug-resistant isolates (44.2%), and 24.3%, respectively; χ^2=9.91, p=0.017). Pan-resistant microorganisms appeared in both groups of the study (10.0% and 3.0%, respectively; p=0.115).

Summary characteristics of microorganisms are presented in table 2.

In group I, the sources of EPI were bile in 18 of 34 cases, sputum (5/34), pleural effusion (5/34), urine (1/34), bacteriemia (3/34), and catheter-associated infection. 2/34) (Figure).

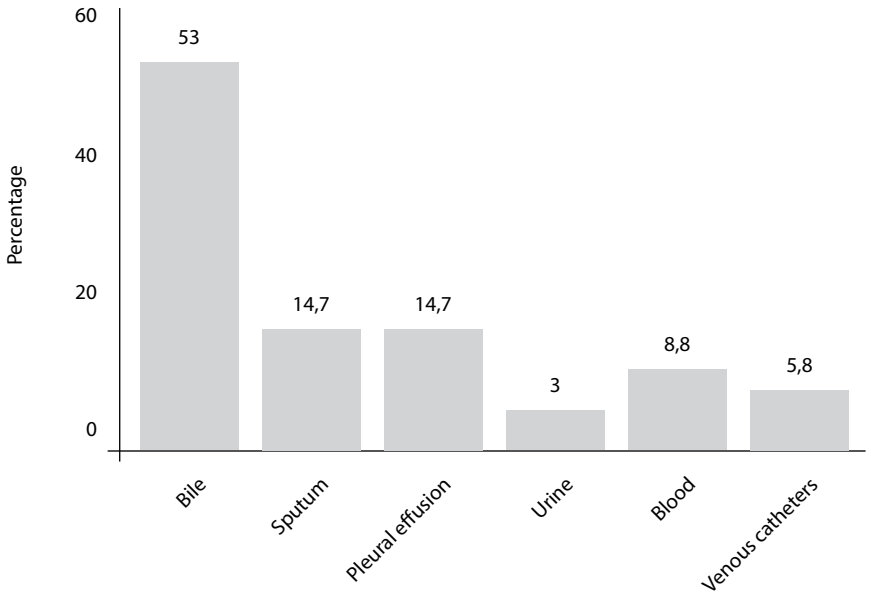
Escherichia coli (44.1%), Klebsiella pneumoniae (11.8%) were dominated in the taxonomic structure of EPI, and its source was bile. Acinetobacter baumannii (14.7%), Pseudomonas aeruginosa (8.8%), and Enterobacter species (8.8%) were mainly isolated in sputum and pleural effusion (Table 3).

Analysis of PI and EPI microbial profile showed that contamination of pancreatic necrosis and/or peripancreatic fluid collections with Escherichia coli and Klebsiella pneumonia was

Table 2
The profile and characteristics of PI pathogens in the study groups depending on the stage of sampling

Microorganisms	Group I, n (%)		Group I, n (%)	
	I stage	II stage	I stage	II stage
Type of microorgamism				
Escherichia coli	8 (26.7)	7 (11.5)	11 (34.3)	8 (12.1)
Klebsiella pneumoniae	4 (13.3)	14 (23.0)	6 (18.8)	16 (24.2)
Enterococcus feacium	6 (20.0)	7 (11.4)	4 (12.5)	10 (15.2)
Staphylococcus aureus	5 (16.7)	4 (6.5)	3 (9.4)	4(6.1)
Staphylococcus saprophyticus	2 (6.7)	–	2 (6.3)	–
Streptococcus haemolyticus	1 (3.3)	2 (3.0)	–	2 (3.0)
Enterobacter species	3 (10.0)	2 (3.0)	5 (15.6)	2 (3.0)
Acinetobacter baumannii	–	12 (19.6)	–	12 (18.2)
Acinetobacter lwoffi	–	2 (3.0)	–	–
Pseudomonas aeruginosa	–	9 (16.0)	1 (3.1)	12 (18.2)
Proteus morganii	1 (3.3)	2 (3.0)	–	–
The type of antibiotic resistance of pathogens				
AMR «–»	24 (76.6)	12 (19.6)	27 (84.4)	20 (30.3)
MDR	4 (13.3)	16 (26.2)	5 (15.6)	28 (42.4)
XDR	2 (6.6)	27 (44.2)	–	16 (24.3)
PDR	–	6 (10.0)	–	2 (3.0)
Total, n	30	61	32	66

Notes: AMR "–" – Antimicrobial resistance, negative; MDR – multidrug-resistant; XDR – extensively drug-resistant; PDR – pan-drug-resistant (by ECDC, 2012).



Extrapancreatic infection localization in patients with severe acute pancreatitis

Table 3
The microbial profile of pancreatic and extrapancreatic infection in patients of Group I

Microorganisms	Pancreatic infection, n (%)		Extrapancreatic infection
	I stage	II stage	n (%)
Escherichia coli	8 (26.7)	7 (11.5)	15 (44.1)
Klebsiella pneumoniae	4 (13.3)	14 (23.0)	4 (11.8)
Enterococcus feacium	6 (20.0)	7 (11.4)	1 (2.9)
Staphylococcus aureus	5 (16.7)	4 (6.5)	2 (5.9)
Staphylococcus saprophyticus	2 (6.7)	–	1 (2.9)
Streptococcus haemolyticus	1 (3.3)	2 (3.0)	–
Enterobacter species	3 (10.0)	2 (3.0)	3 (8.8)
Acinetobacter baumannii	–	12 (19.6)	5 (14.7)
Acinetobacter lwoffi	–	2 (3.0)	–
Pseudomonas aeruginosa	–	9 (16.0)	3 (8.8)
Proteus morganii	1 (3.3)	2 (3.0)	–
Total	30 (100)	61 (100)	34 (100)

associated with biliary infection caused by these microbes. This may indicate their leading role in the development of the infectious process of the pancreatobiliary zone due to translocation from the intestine. Pancreatic infection with Pseudomonas aeruginosa and Acinetobacter baumannii was characterized by the infectious respiratory complications development as a manifestation of nosocomial infection due to a prolonged stay at the ICU. The source of bacteremia was pancreatic necrosis contamination with Staphylococcus aureus and Staphylococcus saprophyticus. The catheter-associated infectious complications were rare (n=2) and were directly associated with colonization of the venous catheters by Acinetobacter baumannii and Enterococcus feacium.

Table 4
Comparison of clinical features of severe acute pancreatitis in studied groups

Characteristics	Group I (n=38)	Group II (n=25)	p- value
delta SOFA*, scores	2 (2–3)	1 (1–2)	<0.001
ICU stay**, days	21.7±3.4	15.8±2.1	<0.001
Hospital stay**, days	44.6±11.5	40.4±15.9	0.26
Mortality, n (%)	11 (28.9)	2 (8.0)	0.044

Notes: *Median (QI–QIII); ** X±m – average ± standard deviation; delta SOFA (The Sepsis-related Organ Failure Assessment).

The correlation analysis revealed a weak direct statistical significant relationship between the presence of EPI and the frequency of detection of antibiotic-resistant microflora, namely XDR-microorganisms at the second stage of material collection (r=0.211, p=0.017). Furthermore, binary logistic regression analysis showed that the presence of EPI increases the probability of development of XDR microorganisms by 2.5 times (R^2=0.61; p=0.019).

The timing of bacteriological verification of PI was statistically and significantly different in the study groups (p<0.001; 95% SI 1.3–3.2). Thus, in group I the primary identification of PI microflora occurred on average by 8.2±2.2 days, and in group II – by 12±2.2 days.

The analysis of the clinical course and treatment outcomes of patients in the study groups revealed a statistically significant difference in the dynamics of multiorgan failure by delta SOFA (p<0.001), duration of stay in ICU (<0.001), and mortality (p=0.044) (Table 4).

It was found that in the group of patients with EPI, there were more pronounced negative dynamics with increasing severity of multiorgan failure by the delta SOFA (median – 2 points (2–3)) vs. without EPI (median – 1 point (1–2); (χ^2=37.5; p<0.001).

The period of stay in the ICU in group I was also statistically and significantly longer (average – 21.7±3.4 days) than in group II (average – 15.8±2.1 days) (p<0.001; 95% SI 4.5–7.3). However, the average period of hospital stay in the study groups did not differ and was 44.6±11.5 bed-days in group I and 40.4±15.9 in group II (p=0.26; 95% CI 10.3–17.6).

Eleven (28.9%) of the 38 patients with EPI died after 14 days, in the group without EPI – 2/25 (8%).

Mortality in the groups differed in the level of significance χ^2=4.04, p=0.044.

In the correlation analysis of the obtained results, it was found that delta SOFA (r=0.77; p<0.001), length of stay in the ICU (r=0.61; p=0.003) and mortality (r=0.24; p=0.044) was statistically significantly correlated with the presence of EPI.

The probability of death in the group with EPI was 10 times higher vs. without EPI (HR 10.4; 95% CI 1.14–94.8; p=0.01).

■ DISCUSSION

Our study revealed that the development of PI was associated with contamination of pancreatic and peripancreatic necrosis Escherichia coli (26.7%), Enterococcus feacium (20.0%), Staphylococcus aureus (16.7%), Klebsiella pneumoniae (18.8%), and 15.6% Enterobacter species), which were subsequently replaced by Klebsiella pneumoniae (23.0% and 24.2%), Acinetobacter baumannii (19.6% and 18.2%) and Pseudomonas

aeruginosa (16.0% and 18.2%). The dynamics of antibiotic resistance development were characterized by a time-dependent increase in the frequency of detection of extensive and pan-resistant microflora. Moreover, it was found that the presence of EPI increased the likelihood of extensive-resistant bacterial strains by 2.5 times.

The main localizations of EPI in our study were bile (Escherichia coli, Klebsiella pneumoniae), respiratory system (Pseudomonas aeruginosa and Acinetobacter baumannii) and blood (Staphylococcus aureus and Staphylococcus saprophyticus).

It was found that the development of EPI contributed to a significant increase in the severity of multiple organ failure, prolonged of stay in the ICU and increase the incidence of hospital mortality rate after 14 days.

■ CONCLUSION

The presence of EPI foci in patients with severe acute infected necrotic pancreatitis negatively affects the effectiveness of antibiotic therapy and contributes to the appearance of extensive drug-resistant strains of microorganisms. Extrapancreatic infection worsens the clinical course of SAP complicated by PI and increases the risk of in-hospital mortality by 10 times.

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