Effects of surgical treatment on 24465 patients with intestinal perforation complicated with septic shock in tertiary hospitals in China from 2017 to 2020: a systematic review

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Keywords: intestinal perforation, septic shock, tertiary hospitals, surgery, China

DOI: https://doi.org/10.21203/rs.3.rs-796292/v1

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Abstract

Background

Intestinal perforation often leads to abdominal infection and is one of the main causes of septic shock. Prompt surgical treatment is an important treatment for this disease. We designed this study to investigate the effects of surgical treatment on patients with intestinal perforation complicated with septic shock in China.

Methods

Tertiary hospitals were enrolled from the China National Critical Care Quality Control Center (China-NCCQC). The data were collected between January 1, 2017 and December 31, 2020. Intestinal perforation includes duodenal perforation, jejunal perforation, ileal perforation, colonic perforation, and rectal perforation. Sepsis 3.0 criteria were used for the diagnosis of septic shock. According to the above criteria, 26747 patients from 247915897 patients were selected. After excluding the missing data of gender, age and discharge mode, 24465 patients were remained.

Results

Patients with intestinal perforation complicated with septic shock in tertiary hospitals in China are more male and older patients. A significant proportion of patients were hospitalized for more than one month. The hospitalization cost per capita of these patients far exceeds the overall hospitalization cost per capita. In the operative group, the hospitalization days were longer. The operative group spent more. However, the incidence of complications was lower in the operative group. Patients with coronary heart disease (CHD) tended to be treated nonoperatively, and patients with systemic lupus erythematosus (SLE) tended to be treated surgically. 20% of the patients discharged against medical advice, 12% of the patients died. The operative group had a higher rate discharging with medical advice and a lower mortality rate.

Conclusions

For intestinal perforation complicated with septic shock in tertiary hospitals in China, patients who had surgery stayed longer and cost more. However, the incidence of complications was lower in the patients who had surgery. At the same time, the rate of discharging with medical advice was higher and the mortality rate was lower in the patients who had surgery.

Background
Intestinal perforation is characterized by rapid onset, severe condition and poor prognosis, which often leads to abdominal infection and is one of the main causes of septic shock(1). Even if we take anti-shock, anti-infection, correct acid-base balance, replenish blood circulation volume and other treatments, it is difficult to prevent the disease from further deterioration(2, 3). Prompt surgical treatment is an important treatment for this disease(4). This study investigated the effects of surgical treatment on patients with intestinal perforation complicated with septic shock in tertiary hospitals in China from 2017 to 2020.

**Methods**

**Study design**

In China, hospitals are classified into 3 grades: community hospitals are defined as primary grade, hospitals that serve several communities are defined as secondary grade, and central hospitals for a certain district or city are defined as tertiary grade. Most patients with intestinal perforation complicated with septic shock were admitted to tertiary hospitals. For above reason, primary hospitals and secondary hospitals were excluded. Tertiary hospitals were enrolled from the China National Critical Care Quality Control Center (China-NCCQC). The data were collected between January 1, 2017 and December 31, 2020.

Intestinal perforation includes duodenal perforation, jejunal perforation, ileal perforation, colonic perforation, and rectal perforation. Sepsis 3.0 criteria were used for the diagnosis of septic shock(5). According to the above criteria, 26747 patients the 247915897 patients were selected. After excluding the missing data of gender, age and discharge mode, 24465 remained.

Based on the data obtained from this survey, we analyzed the basic situation of patients with intestinal perforation complicated with septic shock and the effects of surgical treatment in tertiary hospitals in China.

The study was conducted following the Declaration of Helsinki (as revised in 2013). The central institutional review board approved the trial protocol at Peking Union Medical College Hospital (No. S-K1297), and individual consent for this retrospective analysis was waived.

**Statistical analysis**

Statistical analysis was performed using SPSS 16.0 software (SPSS, Chicago, IL, USA). Hospitalization expenses was expressed as median and quartile M (P25, P75), and compared using the rank test. Other data were expressed as mean ± standard error of mean values and compared using an unpaired Student's t-test. $P<0.05$ was considered to be statistically significant.

**Results**
Gender and age

Among patients with intestinal perforation complicated with septic shock in tertiary hospitals in China, male patients and older patients from 50 to 80 years are more common. Patients in the operative group were more likely to be male and younger than those in the non-operative group \((P<0.05)\) (Table 1).
Table 1
Gender, age, length of stay, hospitalization expenses of patients with intestinal perforation complicated by septic shock in tertiary hospital of China.

| indicators                  | operative | nonoperative | p     | summary               |
|-----------------------------|-----------|--------------|-------|-----------------------|
|                             | n         | %            | n     | %                     | n         | %                     |
| gender                      |           |              |       |                       |           |                       |
| male                        | 12428     | 65.68        | 3518  | 63.47                 | 15946     | 65.18                 |
| female                      | 6494      | 34.32        | 2025  | 36.53                 | 8519      | 34.82                 |
| age (y)                     |           |              |       |                       |           |                       |
| age (y) mean ± SD           |           |              |       |                       |           |                       |
| is 0.0001                   |           |              |       |                       |           |                       |
| < 30                        | 731       | 3.86         | 147   | 2.65                  | 878       | 3.59                  |
| 30 ~ 39                     | 761       | 4.02         | 168   | 3.03                  | 929       | 3.80                  |
| 40 ~ 49                     | 1438      | 7.60         | 413   | 7.45                  | 1851      | 7.57                  |
| 50 ~ 59                     | 2572      | 13.59        | 621   | 11.20                 | 3193      | 13.05                 |
| 60 ~ 69                     | 4427      | 23.40        | 1250  | 22.55                 | 5677      | 23.20                 |
| 70 ~ 79                     | 5251      | 27.75        | 1599  | 28.85                 | 6850      | 28.00                 |
| 80 ~ 89                     | 3363      | 17.77        | 1163  | 20.98                 | 4526      | 18.50                 |
| ≥ 90                        | 379       | 2.00         | 182   | 3.28                  | 561       | 2.29                  |
| length of stay              |           |              |       |                       |           |                       |
| length of stay              |           |              |       |                       |           |                       |
| is 0.0001                   |           |              |       |                       |           |                       |
| 1 ~ 10                      | 5988      | 31.65        | 2871  | 51.80                 | 8859      | 36.21                 |
| 11 ~ 20                     | 7079      | 37.41        | 1421  | 25.64                 | 8500      | 34.74                 |
| 21 ~ 30                     | 3124      | 16.51        | 666   | 12.02                 | 3790      | 15.49                 |
| ≥ 31                        | 2731      | 14.43        | 585   | 10.55                 | 3316      | 13.55                 |
| hospital charges (ten thousand yuan ) | 5.45 | 3.25, 9.38   | 3.59 | 1.43, 7.35            | 5.08      | (2.86, 8.97)          |
| M, Quartile                 |           |              |       |                       |           |                       |
| hospital charges (ten thousand yuan ) |       |              |       |                       |           |                       |
| is 0.0001                   |           |              |       |                       |           |                       |
| < 3                         | 4069      | 21.50        | 2444  | 44.09                 | 6513      | 26.62                 |
Length of stay

Most of the patients with intestinal perforation complicated with septic shock in tertiary hospitals in China were hospitalized within 20 days, while many patients were hospitalized for more than 1 month. The hospital stay in the operative group was longer, with 68.35% of patients staying for more than 10 days, compared with 48.2% in the non-operative group ($P < 0.05$). In the operative group, 14.43% of the patients were hospitalized for more than 30 days, compared with 10.55% in the non-operative group ($P < 0.05$) (Table 1).

Hospital charges

The median hospital charges with intestinal perforation combined with septic shock in Chinese tertiary hospitals is 50,000 yuan, far exceeding the average Chinese hospital charge of 9,800 yuan in 2019. The operative group spent more, with only 21.50% less than 30,000 yuan, and the proportion was as high as 44.09% in the non-operating group ($P < 0.05$). The proportion of those in the operative group who spent more than 90,000 yuan was as high as 26.58%, while that in the non-operative group was only 19.05% ($P < 0.05$) (Table 1).

Complications

The incidence of acute kidney injury (AKI) is the highest among complications of patients with intestinal perforation complicated with septic shock in tertiary hospitals in China, which is close to 10%. The incidence of acute respiratory distress syndrome (ARDS) was 2.86%. The incidence of acute liver injury (ALI) is the lowest, less than 1%. The incidence of complications was lower in the operative group, but there was no statistically significant difference between the two groups (Table 2).

| indicators | operative | nonoperative | $p$ | summary |
|------------|-----------|--------------|-----|---------|
| 3 ~ 6      | 6284      | 1355         | 7639| 31.22   |
| 6 ~ 9      | 3540      | 688          | 4228| 17.28   |
| ≥ 9        | 5029      | 1056         | 6085| 24.87   |

Table 1

| Complications of patients with intestinal perforation complicated by septic shock in tertiary hospital of China. ARDS = acute respiratory distress syndrome, AKI = acute kidney injury, ALI = acute liver injury. |
|---------------------------------------------------------------|
| operative | nonoperative | $p$ | summary |
|-----------|--------------|-----|---------|
| n | % | n | % | |
| ARDS | 532 | 2.81 | 168 | 3.03 | 0.3891 | 700 | 2.86 |
| AKI | 1885 | 9.96 | 552 | 9.96 | 0.9940 | 2437 | 9.96 |
| ALI | 175 | 0.92 | 66 | 1.19 | 0.0780 | 241 | 0.99 |
Basic diseases

Coronary heart disease (CHD) had an impact on whether patients with intestinal perforation combined with septic shock underwent surgery. 7.18% patients in the operative group had CHD, while 9.25% patients in the non-operative group had CHD. There was statistically significant difference between these two groups ($P < 0.05$). Combination of diabetes (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD) and chronic liver failure (CLF) had no effect on whether surgery was performed. Compared with the non-operative group, there were more patients with intestinal perforation combined with septic shock combined with systemic lupus erythematosus (SLE) in the operative group ($P < 0.05$) (Table 3).

|            | operative | nonoperative | $p$     | summary |
|------------|-----------|--------------|---------|---------|
| CHD        | 1358      | 513          | < 0.0001| 1871    |
| DM         | 1433      | 446          | 0.2448  | 1879    |
| COPD       | 1147      | 364          | 0.1695  | 1511    |
| CKD        | 409       | 144          | 0.0546  | 553     |
| CLF        | 840       | 273          | 0.1269  | 1113    |
| SLE        | 47        | 8            | 0.1502  | 55      |

Way of leaving hospital

Among patients with intestinal perforation combined with septic shock in tertiary hospitals in China, 61.92% discharged with medical advice, and 20.14% discharged against medical advice, with a mortality rate as high as 12.08%. The operative group had a higher rate of discharging with medical advice and a lower mortality rate ($P < 0.05$) (Table 4).
Table 4
Way of leaving hospital of patients with intestinal perforation complicated by septic shock in tertiary hospital of China.

|                      | operative | nonoperative | p     | summary |
|----------------------|-----------|--------------|-------|---------|
| n                    | 12412     | 2737         | <0.0001 | 15149   | 61.92   |
| discharge with medical advice | 65.60     | 49.38        |       |         |
| discharge against medical advice | 19.13     | 23.60        | <0.0001 | 4927    | 20.14   |
| death                | 1861      | 1094         | <0.0001 | 2955    | 12.08   |
| summary              |           |              |       |         |

Discussion

Patients with intestinal perforation complicated with septic shock in tertiary hospitals in China are more male and older patients. A significant proportion of patients were hospitalized for more than one month. The hospitalization cost per capita of these patients far exceeds the overall hospitalization cost per capita. In the operative group, the hospitalization days were longer. The operative group spent more. However, the incidence of complications was lower in the operative group. Patients with CHD tended to be treated nonoperatively, and patients with SLE tended to be treated surgically. 20% of the patients discharged against medical advice, 12% of the patients died. The operative group had a higher rate of leaving hospital with medical order and a lower mortality rate.

Septic shock refers to the shock caused by severe infection caused by microorganisms and their toxins. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure of 65 mmHg and serum lactate level greater than 2 mmol/L in the absence of hypovolemia(6). Septic shock progresses rapidly and has a high fatality rate(7, 8). It has been reported that the incidence of septic shock is increasing year by year(9, 10), and clinical manifestations such as decreased blood pressure and dampness and cold of skin are often present. With the prolongation of time and the aggravation of the disease, septic shock often progresses into multiple organ dysfunction syndrome, which poses a great threat to the life safety of the patients(11). The 90-day mortality of patients with septic shock was as high as 49.1%, among which multiple organ dysfunction syndrome was an important cause of death(12). How to reduce the mortality of patients with septic shock has become a hot issue in the field of critical care medicine. Removal of infective foci is an important method to reduce the mortality of septic shock(13). Intestinal perforation is a common cause of septic shock(14). Intestin is the key organ for the occurrence of septic shock, and enterogenous endotoxemia is closely related to the occurrence of septic shock and multiple organ dysfunction syndrome (MODS)(15). Intestinal perforation can cause acute diffuse peritonitis, resulting in water and electrolyte imbalance and acid-base imbalance, and secondary abdominal infection. In severe cases, a large amount of toxic substances are absorbed by peritoneum. The clinical manifestations of septic shock occurred within 12 ~ 24 h, and it can develop into MODS in a short time, and the fatality rate significantly increased(16). For patients of
gastrointestinal perforation with associated septic shock, time from admission to initiation of surgery for source control is a critical determinant, under the condition of being supported by hemodynamic stabilization(17). In this study, we investigated the basic information of patients with intestinal perforation combined with septic shock in tertiary hospitals in China from 2017 to 2020 and the effect of surgical intervention to clarify the epidemiological data of such patients, with a view to improving the treatment of septic shock caused by intestinal perforation.

Intestinal perforation is closely associated with frequent over-fatigue, over-satiety, and fasting, which are more common in male. A 66% of the patients who underwent surgery for an intestinal perforation at a single institution in Korea were male(18). In our study, the proportion of males in patients with intestinal perforation combined with septic shock in tertiary hospitals in China was as high as 65.18%.

Due to the degeneration of organ function, low immunity and weak constitution in the elderly, the incidence of intestinal perforation in the elderly is on the rise. The mean age of patients who underwent surgery for an intestinal perforation at a single institution in Korea was 66 years(18). The median age of newly diagnosed colon cancer cases initially presenting with perforation or obstruction at a general hospital of Taiwan was 72 years(19). In our study, most patients with intestinal perforation combined with septic shock were between the ages of 50 and 80 years. According to a report by China's National Health Commission, the average life expectancy in China in 2019 was 77.3 years. The above factors can explain why the proportion of the population over 80 years old decreased.

Average length of stay for children hospitalized with severe sepsis or septic shock was 24 days(20). The median hospital length of stay for acute colonic perforation patients who received rapid source control laparotomy was 20 days(21). The length of stay for patient who received omental patch repair for gastric or duodenal perforation was 15.5 days(22). In our study, most patients were hospitalized within 20 days, although many patients were hospitalized for more than a month. The treatment effects of patients with intestinal perforation complicated with septic shock in tertiary hospitals in China is significant, and the room for improvement is also large. Compared with the non-operative group, the hospital stay of the patients with intestinal perforation complicated with septic shock in the operative group was longer. This may be because doctors need time to watch the wound heal after the patient has undergone surgery.

Due to the complex and critical condition of intestinal perforation complicated with septic shock, the treatment is extremely difficult and costly. Average hospital charges for children hospitalized with severe sepsis or septic shock were $314,950(20). The median charge for a septic shock hospitalization of a large academic hospital was $98,583 in the United States(23). The median compensation for the colon perforation during colonoscopy was $9335.47(24). In our study, the median hospital charges with intestinal perforation complicated with septic shock in tertiary hospitals in China are 50,000 yuan, far more than the 9,800 yuan per person spent on hospitalization in 2019 in China. Patients with the treatment cost of more than 90,000 yuan are as high as 24.87%. The hospital charges with intestinal perforation complicated with septic shock is high, so efforts should be made to improve the treatment level in order to reduce the hospital charges. Compared with the non-operative group, the hospital charges
of the patients with intestinal perforation complicated with septic shock in the operative group were higher. This may be because the operation of intestinal perforation combined with septic shock is complicated and difficult, so the operation itself is expensive.

Organ dysfunction is a hallmark clinical event of septic shock, and multiple organ dysfunction is the most severe outcome of the progression from simple infection to severe sepsis and septic shock. Sepsis-induced organ dysfunction often manifests as MODS, which is the main cause of death of patients with intestinal perforation complicated with septic shock. AKI, ARDS and ALI are the most common manifestations of MODS. AKI was present in 71% of patients of severe sepsis and septic shock in the intensive care units of Trinidad, with renal replacement therapy being used in 30% of cases(25). Compared with lower gastrointestinal perforation, patients with septic shock from upper gastrointestinal perforation are more likely to develop AKI, more likely to require CRRT treatment, longer mechanical ventilation, and longer ICU stay(1). AKI is very common in septic shock from severe burns. Mortality is unacceptably high in patients of septic shock from severe burns who develop AKI requiring renal replacement therapy(26). In our study, the incidence of AKI in MODS caused by intestinal perforation complicated with septic shock was the highest, close to 10%. Mechanical ventilation was required in 84% of cases of patients of severe sepsis and septic shock in the intensive care units of Trinidad(25). In our study, the incidence of ARDS was 2.86%. The incidence of ALI was the lowest, less than 1%. The incidence of complications was lower in the operative group, which supported the surgical treatment of intestinal perforation complicated with septic shock.

Adverse cardiovascular events after noncardiac surgery are associated with increased long-term morbidity and mortality. Peri-operative cardiovascular risk is particularly high in individuals with underlying cardiovascular disease(27). Patients with CHD tended to be treated nonoperatively, and patients with SLE tended to be treated surgically. Due to concerns about perioperative acute coronary events and anticoagulant and antiplatelet therapy therapy, non-operative treatment is often preferred for patients with intestinal perforation complicated with septic shock with CHD. Although SLE patients present higher frequency of postoperative complications and mortality compared with non-SLE patients(28), there were more patients with intestinal perforation combined with septic shock combined with SLE in the operative group. The reason for above phenomenon may be that SLE is an autoimmune disease, and patients with SLE with septic shock have a low chance of self-healing, which is likely to lead to more positive treatment.

The in-hospital mortality of patients meeting the sepsis-3 septic shock criteria was 40.9% (29). In our study, 20% of the patients discharged against medical advice, 12% of the patients died. Discharge against medical advice refers to the patient's family members' voluntary leave hospital due to the serious condition and high cost of the patient. Combined with the fact that most of the patients discharged against medical advice because of poor treatment effect, the true mortality rate is likely to be underestimated. There is still much room for improvement in the treatment of patients with intestinal perforation complicated with septic shock in tertiary hospitals in China.
Patients with intestinal perforation will appear pancreatic fluid, bile and other gastrointestinal fluid exudation phenomenon, inducing chemical peritonitis, and due to the rapid growth of pathogenic bacteria, will lead chemical peritonitis to bacterial peritonitis. In the late stage of intestinal perforation, symptoms of secondary septic shock appeared, including decreased blood pressure, severe infection in the abdominal cavity, massive fluid extravasation, insufficient circulating blood volume, coupled with bacterial toxins and inflammatory mediators induced by them, resulting in peripheral vascular dilation and decreased diastolic blood pressure. When the peripheral circulation fails, the peripheral resistance is further reduced, exacerbating the decrease in effective circulating blood volume, and ultimately leading to fatal shock. We believe that even if we take anti-shock, anti-infection, correct acid-base balance and replenish blood circulation capacity, it is difficult to prevent the further deterioration of the condition when such a severe patient comes to hospital. Measures to reduce the incidence of such severe diseases still emphasize timely surgical exploration rather than delayed observation. This study confirmed that the rate of discharging with medical advice was higher and the mortality rate was lower in the operative group. The above results further support the surgical treatment of patients with intestinal perforation complicated with septic shock.

The present study has some limitations. First, this study is purely descriptive. Second, there were too many interfering factors in this study to determine whether the difference in outcome caused by surgical treatment was related to bias factors.

Conclusions

Patients with intestinal perforation complicated with septic shock in tertiary hospitals in China are more male and older patients. Such patients have a long hospitalization time, with a considerable proportion of patients hospitalized for more than 1 month. The hospital charges of such patients are high, and the proportion of patients who spend more than 90,000 yuan is as high as 24.87%. The operative group stayed longer and cost more. However, the incidence of complications was lower in the operative group. At the same time, the rate of discharging with medical advice was higher and the mortality rate was lower in the operative group.

Abbreviations

China National Critical Care Quality Control Center = China-NCCQC, acute kidney injury = AKI, acute respiratory distress syndrome = ARDS, acute liver injury = ALI, coronary heart disease = CHD, diabetes = DM, chronic obstructive pulmonary disease = COPD, chronic kidney disease = CKD, chronic liver failure = CLF, systemic lupus erythematosus = SLE, multiple organ dysfunction syndrome = MODS.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The trial protocol was approved by the Central Institutional Review Board at Peking Union Medical College Hospital (NO.: S-K1297) and individual consent for this retrospective analysis was waived. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Consent for publication

All authors have seen and agreed with the contents of the manuscript, and the manuscript has been submitted solely to this journal and is not published, in press, or submitted elsewhere.

Availability of data and material

The datasets supporting the conclusions of this article are included within the article.

Competing interests

The authors declare that they have no competing interests.

Funding

This research was supported by National Key R&D Program of China (grant number 2020YFC0861000) and National Natural Science Foundation of China (No. 81801901).

Authors’ contributions

XZ, DWL & YL conceived and designed the experiments. LW, XDM, HWH, LXS, YHG, GLS & YW analyzed the data, and wrote the manuscript. AND, LW, XDM & XZ edit and revised the manuscript. All authors read and approved the final manuscript.

Acknowledgment

We thank Wei Huang for her technical support and editorial assistance.

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