



A comparative analytical study on outcome of secondary peritonitis using Mannheim's peritonitis index in geographically diverse Indian patients

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ABSTRACT

Objective: Secondary peritonitis is caused by infection of the peritoneal cavity due to perforation of the alimentary tract. Mannheim's peritonitis index (MPI) is a prognostic scoring system that predicts outcomes in peritonitis. Increasing MPI scores correlate with poor outcomes and mortality. The objective of this study is to evaluate the effectiveness of MPI-based prognosis and its impact on Indian patients with secondary peritonitis.

Material and Methods: For understanding the effectiveness of the MPI scoring system, a cross-sectional data analysis of published studies on secondary peritonitis from 10 geographical locations in India was performed. The 10-site study results were compared with unpublished in-house study data for individual MPI parameters to analyze any variations of MPI score-based predictions across a diverse Indian population. Patients were divided into risk groups on the basis of MPI scores: <21 mild, MPI= 21-29 moderate, MPI> 29 severe risk.

Results: We observed a significant correlation between mortality with age and gender as reported worldwide. Site of perforations were prevalent in the upper alimentary tract with the majority being gastro-duodenal for the Indian population as opposed to distal parts in the western population. Higher lethality in India is often associated with evolution time, organ failure, and sepsis due to delayed presentation and poor management.

Conclusion: MPI scoring is effective in predicting risk across geographically diverse Indian populations. The sensitivity and specificity of MPI scores are more reliable and a score >29 specifically recommends aggressive resuscitation & monitoring of patients, initiation of broad-spectrum antibiotics, and intensive care support to reduce mortality and morbidity.

Keywords: Secondary peritonitis, Mannheim's peritonitis index, infection, mortality

INTRODUCTION

Peritonitis is the inflammation of the peritoneum caused by the damage of intestinal lining and associated infection (1,2). Clinically, peritonitis is classified as primary, secondary, or tertiary peritonitis (1,3). Primary peritonitis is rare and often caused by extra peritoneal bacterial/foreign bodies' translocation and hematogenous dissemination (3,4). Secondary peritonitis is the most common form of peritonitis caused by spontaneous perforation of the gastrointestinal tract, intestinal ischemia or iatrogenic exposure resulting in direct contact with a peritoneal contaminant (1,2,5). Since abdominal integrity is compromised, secondary peritonitis is often associated with poly-microbial infection (5,6). Secondary peritonitis accounts for 1% of emergency admissions and is the second leading cause of sepsis resulting in a global mortality rate of 6% (2). Secondary peritonitis is a very common surgical emergency in India with a mortality rate of ~9% to 16% as per recent studies across India (7-9). Despite improved understanding of pathophysiology, advanced surgical techniques and antibiotic availability, mortality due to secondary peritonitis is higher in Indian population in comparison to western world (10,11). Consequently, identifying better scoring systems for early evaluation and categorization of the patients with secondary peritonitis is required for better resuscitative measures.

Here, we used Mannheim's peritonitis index (MPI), which had been developed and validated by Wacha et al. and others, for scoring the severity and outcomes of the study performed with 110 subjects of secondary peritonitis from the northeastern

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region of India (12-14). MPI based system is often advantageous over other scoring systems for better management of the disease, patient segregation, prognostic reliability and specificity (15,16). Additionally, we performed a comparative analysis of studies with secondary peritonitis throughout India using MPI based scoring parameters and provided a bird's eye view regarding risk factors of the disease (17-26). The purpose of the study was to understand the variability in outcome due to MPI score parameters across Indian patients with diverse background and predict the overall effectiveness of the MPI scoring system used for accessing risk groups in secondary peritonitis. We observed significant increase in morbidity and mortality in patients with increasing MPI scores. There is less variability among individual parameter score and outcomes in terms of mortality. Together, our study convenes an Indian subcontinent specific risk evaluation of secondary peritonitis and supports the usage of the MPI scoring system to predict patient outcomes.

MATERIAL and METHODS

Study Details

The Institute study protocol was reviewed and approved by REB (research ethics board). All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained by all subjects. The study was conducted in the department of surgery in a regional institute of the northeastern part of India as a cross sectional study for two years (2018-2020). Patients with a diagnosis of secondary peritonitis were placed under inclusion criteria. Exclusion criteria included patients with primary peritonitis, tertiary peritonitis, patients who had not undergone surgery, patients with post-operative anastomotic dehiscence or leak, peritonitis due to trauma to abdomen, patients with acute appendicitis (without perforation) and patients unwilling to take part in the study. One hundred and ten patients enrolled underwent exploratory laparotomy within the study period. Independent study variables for MPI scoring system included: age in

completed years, sex, malignancy (present/absent), organ failure (present/absent), evolution time (>24 hours/<24 hours), extension of peritonitis (localized/diffuse), origin of sepsis (non-colonic/colonic), character of exudates (clear/faecal/purulent) as described previously (12-14). We also curated available published data of MPI based studies from India for our comparative analysis (17-26).

Parameters for MPI Evaluation

A pre-designed, pre-tested proforma which consisted of particulars of the patients, symptomatology, general physical examination, abdominal findings & other systematic examinations, laboratory investigations, intra-operative findings & post-operative outcomes were taken into account for MPI scoring (Table 1). Criteria published by Deitch EA were utilized for organ failures. Renal failure assessment was determined as serum creatinine >177 mmol/L OR serum urea >16.7 mmol/L OR oliguria (urine output <20 mL/hr), pCO₂> 50 mm Hg OR pO₂< 50 mm Hg for respiratory failure, >24 hours of paralysis OR mechanical ileus for intestinal obstruction and systolic BP< 90 mmHg OR reduction> 40 mm Hg from baseline for shock. Malignancy was categorized as known malignancy or gross or histo-pathological features of malignancy including perforation of the malignant gastric ulcer, suspicious perforation of a colonic mass and obstruction due to distal malignant growth, perforation of proximal bowel. For evolution time criteria was set for <24 hours/>24 hours between onset and surgery. Source of perforation was demarcated as non-colonic/colonic based on exploratory laparotomy. Individual scores of each parameter of each patient were added to calculate MPI. Divisions of the patients into three categories were done as follows: MPI< 21: mild risk group, MPI= 21-29: moderate risk group, MPI> 29: severe risk group.

Biochemical and Radiological Study

Routine haematological and urine examinations were performed for secondary peritonitis patients. Diagnoses of secondary peritonitis were confirmed routinely by erect

Table 1. Representing study variables and adverse factors used for scoring Mannheim's peritonitis index for secondary peritonitis studies

Study variable	Adverse factors	Score	Favorable factors	Score
Age	>50 years	5	<50 years	0
Sex	Female	5	Male	0
Organ failure	Present	7	Absent	0
Evolution time	>24 hours	4	<24 hours	0
Malignancy	Present	4	Absent	0
Source of perforation	Non-colonic	4	Colonic	0
Extension of peritonitis	Diffuse	6	Localized	0
Character of exudate	Purulent fecal	6 12	Clear	0

radiograph of the abdomen. In selected cases, ultrasonography (USG) and axial computerised tomography (CT) scan of the whole abdomen were done.

Surgery and Follow Up

Initial resuscitative measures included keeping the patient nil per orally (NPO), intravenous fluid, antibiotics and analgesics, correction of electrolyte imbalance (if any), abdominal decompression by putting nasogastric tube and Foley's catheterisation. Patients who were fit for surgery were managed by exploratory laparotomy for peritoneal toileting and repair of perforation. Intra-operative finding of perforation in a patient with peritonitis were taken as gold standard for secondary peritonitis. Post-operatively, all of the patients were followed up until their discharge or death.

Statistical Analysis and Reproducibility

Collected data were tabulated using Microsoft Excel and analysed accordingly using Graphpad Prism version 8.3.02 (GraphPad Software, CA, United States). For comparative analysis, available data were treated as non-parametric for adverse factors. Independent t-test using Mann-Whitney method was used for statistical significance. One way-ANOVA using Kruskal-Wallis method for multiple groups was used for statistical significance. Chi-square test and Fisher's exact test were performed for correlation among MPI categories for statistical significance. For in-house study data, n= 110 patients. ROC curve was plotted using MedCalc® Statistical Software version 20.112 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2022). DeLong et al. method and binomial exact with 95% confidence interval regarding AUC were performed for statistical significance, and $p < 0.05$ was considered as statistically significant.

RESULTS

Occurrence and Associated Mortality Due to Secondary Peritonitis in India

In order to evaluate secondary peritonitis for a group of 110 patients from the study institute, we used Mannheim's peritonitis index (MPI) scoring system. We utilized an 8-parameter-based scale deployed in all studies for assessing MPI scores as described in study detail. In order to understand the prevalence and pattern of secondary peritonitis across India, we compared our in-house study with 10 other published studies that had used MPI scoring system from various states of India (17-26). Studies from different geographical locations were selected to have an idea about the epidemiological diversity of secondary peritonitis across India (Figures 1A, 1B). As we further subcategorized patients as per sex, we observed a preponderance of male patients compared to female that were significantly correlated in all studies (Figure 1C). We observed a higher lethality rate due to secondary peritonitis in

the Indian population up to ~32% in comparison to current lethality rate of 6% worldwide (Figure 1D) (2).

Correlation of Mortality with Factors Contributing to MPI Score Among Various Studies

We accessed the MPI based studies from 11 sites as stated above and categorized the outcome (percentage of death) against individual factors affecting MPI scores as per data availability. The parameter for age (<50 and >50 years), indicated significantly higher incidence of peritonitis in age groups lower than 50 (Figure 2A). As reported by others, we also observed an increased death rate (11-33%) in patients group with age >50 years (Figure 2B) (27-29). Interestingly, we found significant association between increased duration of hospital stay with age >50 years group in the in-house institutional study (Figure 2C).

We found a higher male to female ratio in patients with secondary peritonitis (Figure 2D). Provided sex to be an adverse factor, we checked for mortality. Among the available datasets, with an exception for Pune and Kerala (South Western India), there was increase mortality (9-56%) in female patients which is also reflected in the in-house study (Figure 2E).

Source of perforation is an important parameter which dictates the outcome of secondary peritonitis. We interrogated the data from seven studies for site of perforations which is directly related to the severity of peritonitis. We found that maximum incidents of peritonitis occurred at the sites of gastroduodenal (34-80%), ileal (6-53%) and appendicular (4-47%) region while lesser incident occur at jejunal (4-7%), colonic (2-10%) and other non-alimentary sites (1-10%) (Figure 2F). Among the available datasets, we were able to check the mortality of patients with respect to perforation site. We found that gastroduodenal perforations had lesser incident of deaths (~10%) while ileal (13-28%) and colonic (16-50%) perforations had higher incidence of death (Figure 2G). Albeit, we observed a significant correlation of death associated with ileal and gastroduodenal perforations. We checked the extension of peritonitis and character of exudate parameters and found higher mortality with diffused form (13-36%) of peritonitis (Figure 2H). Both purulent (4-60%) and feculent (36-100%) natured exudates showed higher death compared to clear exudates (0-12%) in the patients (Figure 2I). Presence of malignancy could not be considered as an independent parameter. Given the lower number of patients with malignancy, we observed variability in death rates (0-100%) of the patients with malignancy and also higher deaths in patients without malignancy (Figure 2J). The parameters for presence of organ failure and high evolution time (>24 hr) contributed significantly towards higher mortality rates. Mortality rate for organ failure was 22-75% and evolution time was 18-32% respectively among the available study locations (Figure 2K and 2L).

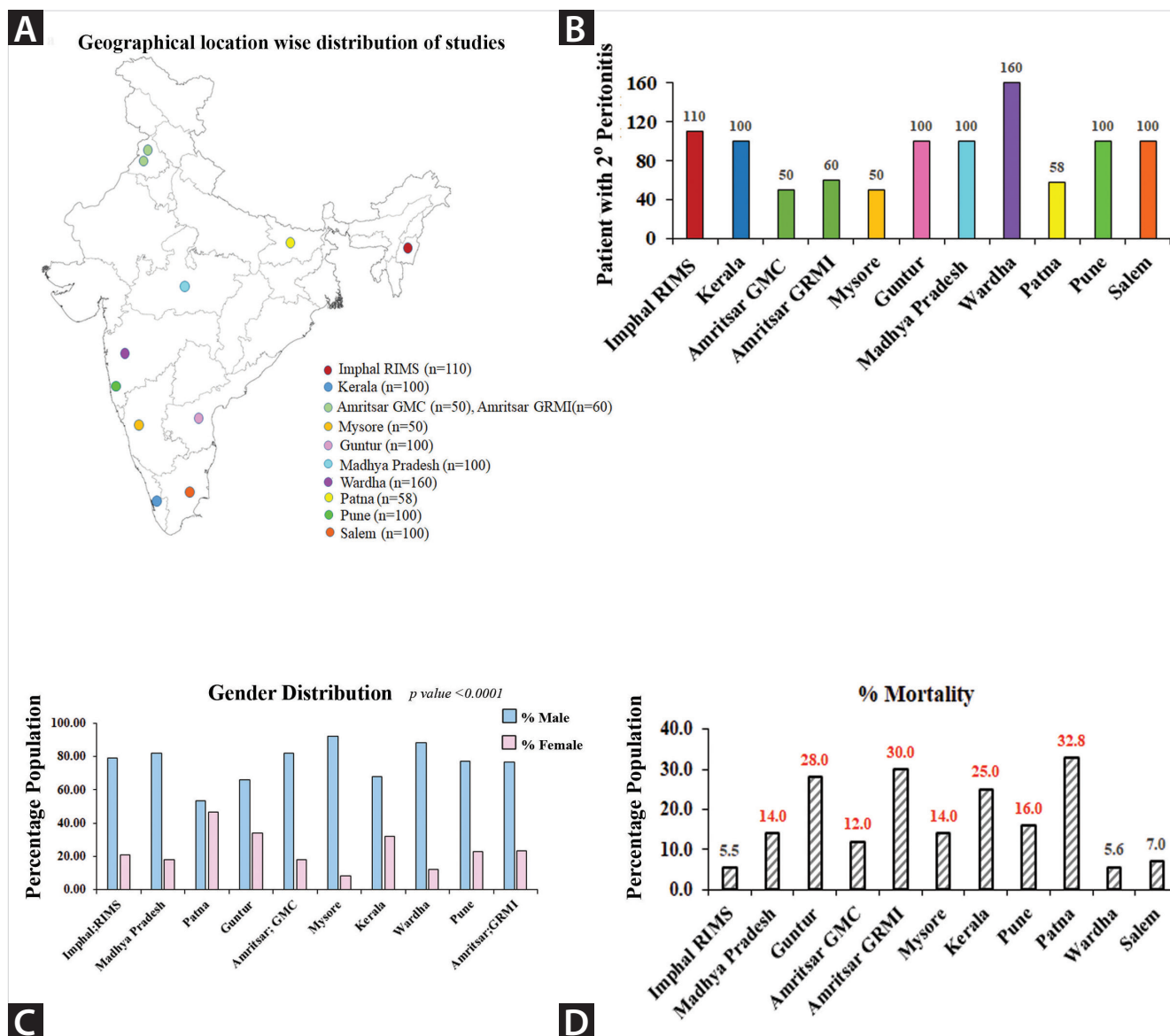


Figure 1. A. Geographical, location wise distribution of the studies on secondary peritonitis from India used in the study. **B.** Graphical representation of the number of patients in case studies of secondary peritonitis used in the study. **C.** Study wise distribution of the percentage population of male and female subjects. Mann-Whitney test was performed for statistical significance where *****p* < 0.0001. **D.** Percentage mortality was calculated for all available data sets.

Identifying Key Factors Affecting MPI Scores, Treatment Procedures and Outcomes of In-House Study from North-East India

For surgical procedures, Graham’s patch repair, primary repair of perforations, appendectomy, resection and anastomosis, gastrojejunostomy and right hemi-colectomy were performed (Figure 3A). This is relatable with the site of perforation statistics reported earlier in the study. Appropriate MPI scoring system of <21 (mild risk), 21-29 (moderate risk) and >29 (high risk) was adapted for in-house study patients (30,31) (Figure 3B). In the in-house study, the mean MPI value was 22.07, minimum being 10 and maximum being 43. We observed significant correlation

for each study variables except the source of perforation (Figure 3C). Interestingly, we observed a significant positive correlation between the severity of complications and higher MPI scores for patients (Figure 3D). We found an increased mortality rate (21-29 MPI score 5.5%, >29 MPI score 25%) with higher MPI score associated with major complications like faecal fistula, chest infections etc. (Figure 3E). In order to gauge the sensitivity, specificity and best cut-off for MPI score, we used receiver operating characteristic (ROC) curves against mortality and morbidity (complications) (Figures 2F, 2G). The area under the curve (AUC) with respect to mortality and morbidity were 0.911 and 0.749 respectively; indicating MPI an effective scoring system.

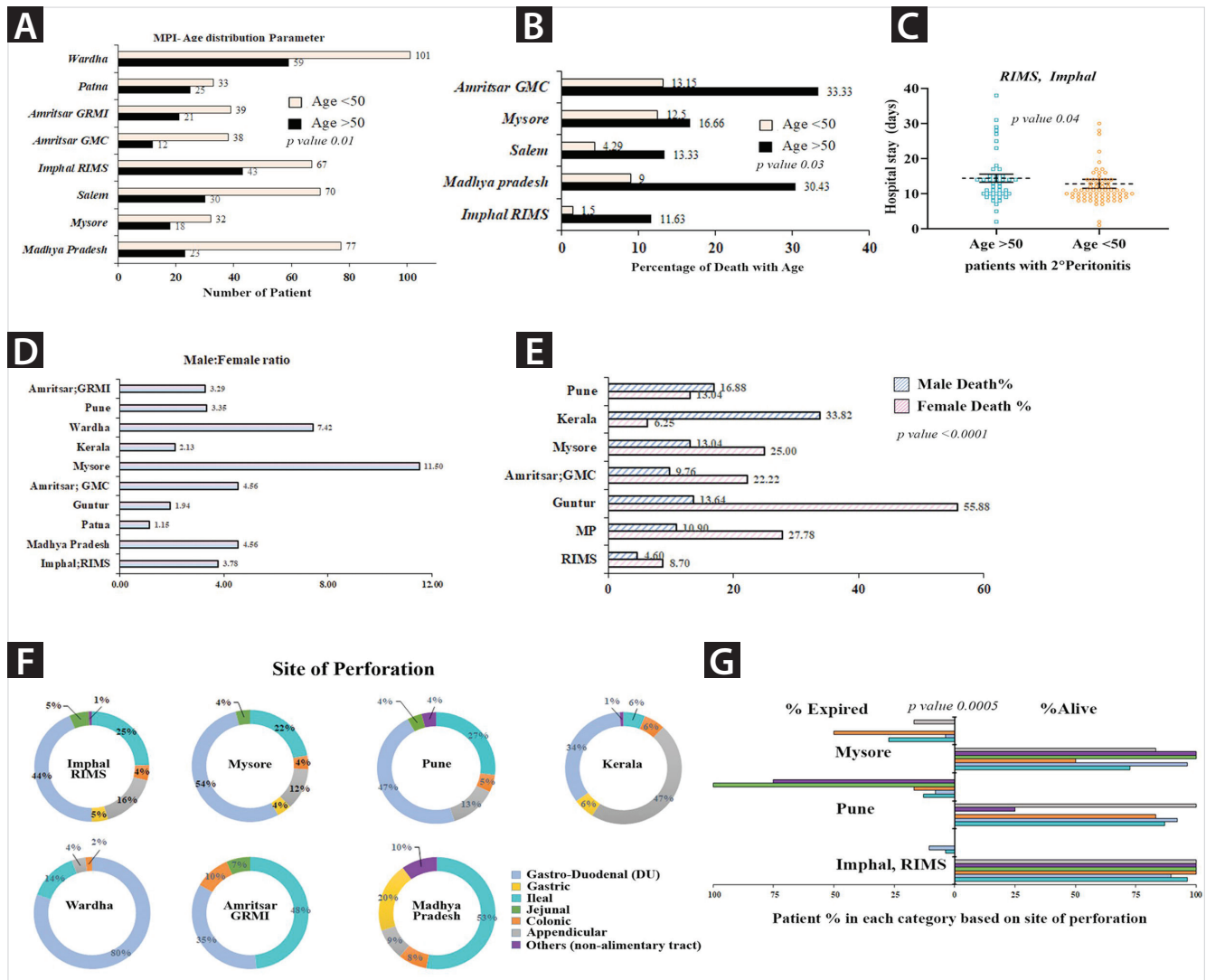


Figure 2. A. Graphical representation of age distribution under various studies. Mann-Whitney test was performed for statistical significance where $*p=0.01$. B. Percentage mortality was plotted for indicated groups (>50 years and <50 years). Mann-Whitney test was performed for statistical significance, where $*p=0.03$. C. Hospital stay for patients in the number of days were plotted for indicated groups from the in-house study. Mann-Whitney test was performed for statistical significance where $*p=0.04$. D. Male and female percentage population was plotted as a ratio (male:female) for indicated studies. E. Death percentage was plotted for indicated groups male and female. Chi-square test for trend was performed for statistical significance, where $*p<0.0001$. F. Representation of the indicated perforation sites due to the incidence of secondary peritonitis from indicated studies. G. Patient population mortality based on sites of perforation were plotted as indicated for multiple groups. Kruskal-Wallis test was performed for statistical significance, where $***p=0.0005$.

DISCUSSION

Although MPI scoring system was deemed better or similar to other scoring systems like qSOFA (quick sequential organ failure assessment), APACHE II (acute physiological assessment and chronic health evaluation), and etc. while predicting mortality and morbidity in secondary peritonitis, subsequent sepsis related complications do not reflect well to these scoring systems (26,29,32-35). Since the APACHE II and SAPS scoring system measures permanent biochemical changes and organ

insufficiency for predicting mortality and morbidity, it becomes unreliable to patients developing septic shock post operatively within 24 hours (36). Biochemical parameters like IL-6, C-reactive protein and caspase three levels can often provide leverage for surgical decisions and should be considered alongside the scoring systems (37). We followed the meta data analysis study of Billing et al. for our comparative analysis (30). In our assessment of MPI based studies of secondary peritonitis in Indian population we found some interesting trends and outcomes.

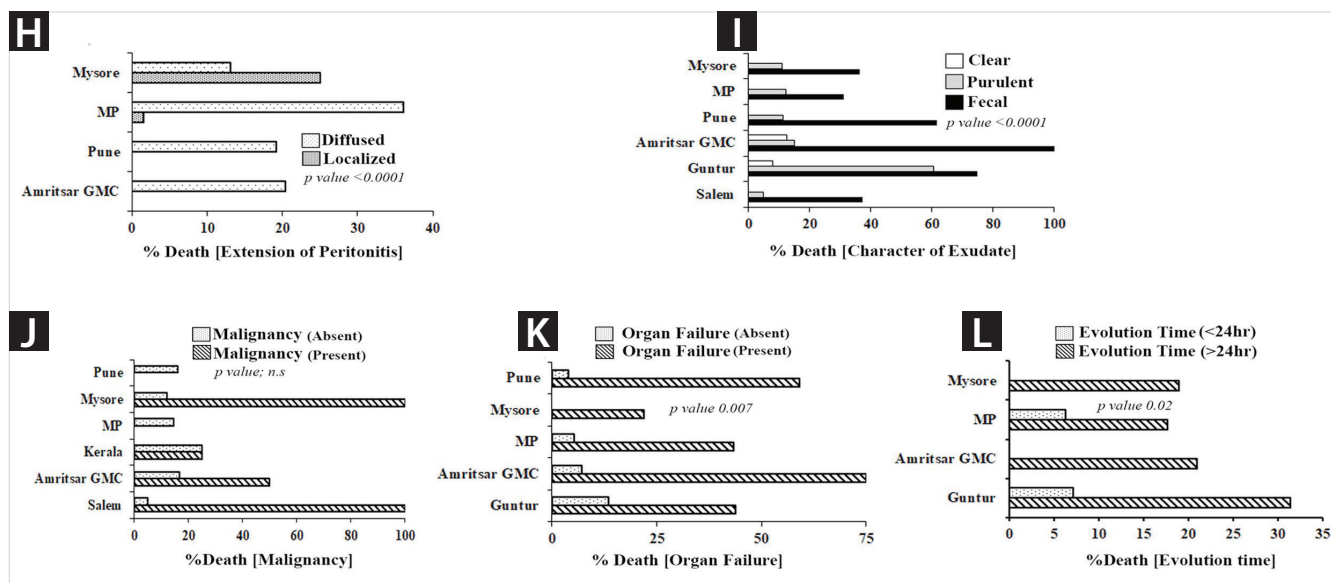


Figure 2 (continue). H. Mortality due to extension of peritonitis as per indicated groups. Chi-square test for trend was performed for statistical significance, where *p< 0.0001. I. Mortality in patient based on character of exudates were plotted as indicated for multiple groups. Kruskal-Wallis test was performed for statistical significance, where ****p< 0.0001. J. Mortality in patients based on malignancy (present or absent) were plotted for indicated studies. Mann-Whitney test was performed for statistical significance, where n.s stands for non-significant. K. Patient mortality based on organ failure (present or absent) were plotted as indicated. Mann-Whitney test was performed for statistical significance, where *p= 0.007. L. Patient mortality based on evolution time (>24 hours or <24 hours) was plotted as indicated. Mann-Whitney test was performed for statistical significance, where *p= 0.02.

For example, we observed a higher hospital admission for peritonitis patients (~1.5-2 folds) with age <50 years for all the studies. However, the trend in mortality showed an increased death rate (~11-33%) among various studies for patients with age >50 years as observed by others (28,29). Similarly, we observed a biased sex ratio with >~2-fold higher admission for male patients. Opposing, the death rates were higher for females (~2 to 5 folds) as compared to males. The results indicates that MPI scoring system is superior in predicting outcomes even under a biased inclusion of patients and showed similar trends worldwide.

For the site of perforations within the alimentary canal, we found most of the perforations to be of gastroduodenal (40-80%) and ileal (6-48%) origin. We anticipate that infection with helicobacter, acid peptic disorder in the gastroduodenal region while typhoid infections, tuberculosis and trauma in the small bowel (ileal) results in the initiation of the disease (38-40). Given intestinal tuberculosis and typhoid enteritis are common in India, we anticipated a high number of perforations in the upper parts of the alimentary canal as opposed to distal parts in European and North American population (40-42). Appendicular perforations were also common in all studies (5-40%). Interestingly, in the in-house data, we observed more female patients (11 out of 18) with appendicular perforations in comparison to males. Considering the site of the upper alimentary tract, death rates varied from ~10-28%.

Factors like diffused peritonitis and faecal nature of exudates correlated significantly with increased death rates. However, we did not find association of malignancy with death in many studies. We found an obvious association of increased mortality with organ failure and evolution time of the disease. Delayed admission of patients results in sepsis and eventual organ failures in cases of peritonitis (3,5). Unfortunately, even post-surgery, lethality occurs due to septicaemia, disease acuity and organ failure (43).

For the in-house study data, we categorized the patient MPI score as <21 (low), 21-29 (moderate) and >29 (high). We observed a similarity in patient density under MPI categories in various states indicating a trend of low number of patient (<30%) in the category >29. This is relevant as mostly younger generations suffer from secondary peritonitis in India. We observed significant correlation of MPI categories with adverse factors that affect the MPI scores except the site of perforation indicating its effectiveness over our study. Owing to more prevalent non-colonic perforation and lower colonic perforations, it was difficult to conclude any association for the site of perforation. We found more complications like wound infections, faecal fistula and pulmonary complications in patients having >29 MPI score which correlated with increasing mortality in the same group. Finally, to estimate the performance regarding true predictability of MPI scoring system on our in-house data, ROC curves regarding mortality and morbidity were used.

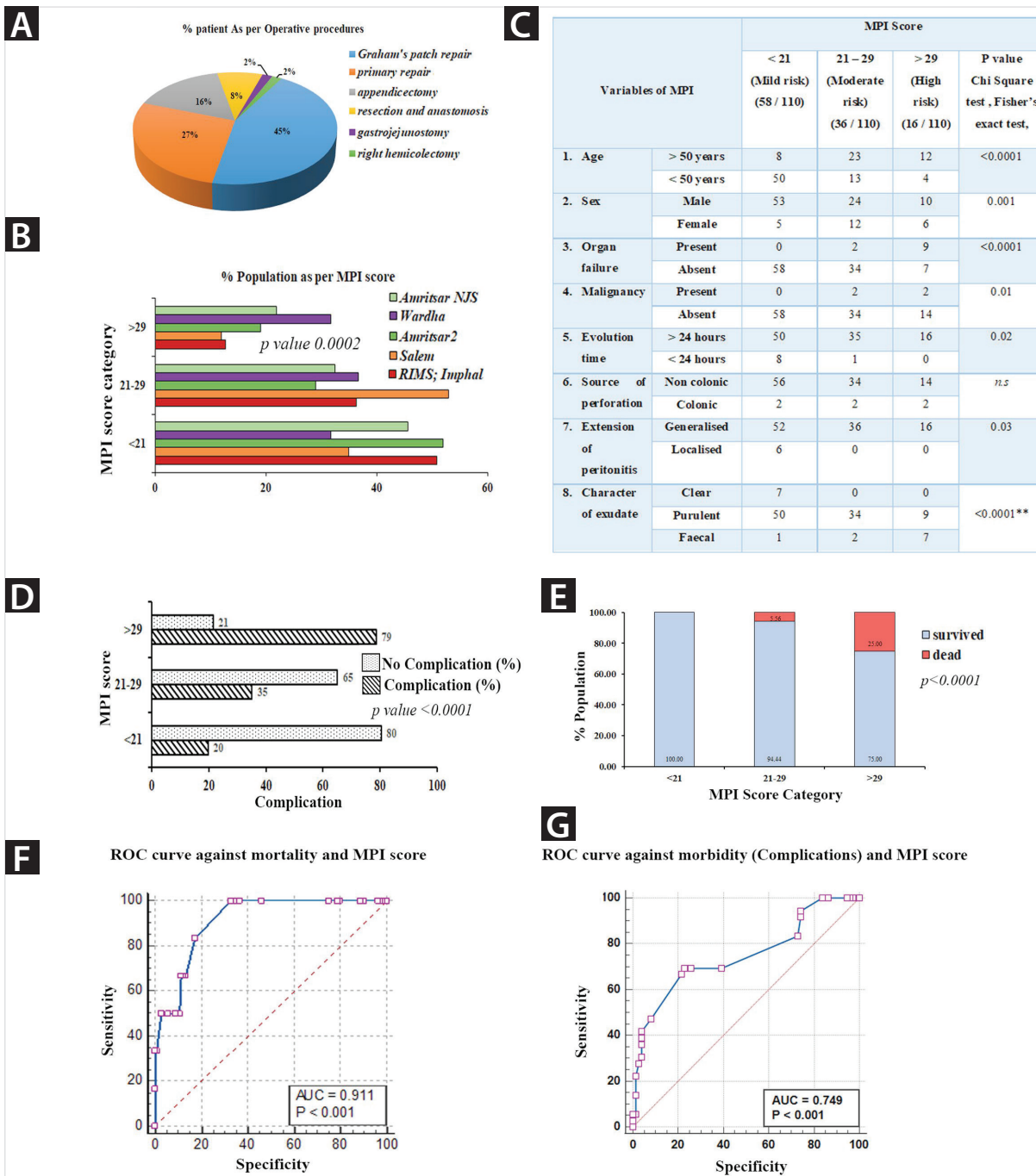


Figure 3. A. Patient percentage under various operative procedure on patients with secondary peritonitis from in-house study. B. Patient percentage under various MPI score categories were plotted. Chi-square test for trend was performed for statistical significance between categories; where *** $p = 0.0002$. C. Table showing patient numbers belonging to indicated categories under MPI score for in-house study. Chi-square test for trend was performed for statistical significance between categories. **Fisher's exact test was performed by combining two groups where Chi-square assumptions for minimal expected value failed. n.s is non-significant. D. Percentage patient with complication was plotted against MPI score categories. Chi-square test was performed for statistical significance, where **** $p < 0.0001$. E. Percentage mortality (dead and survived) was plotted against MPI categories. Chi-square test was performed for statistical significance, where **** $p < 0.0001$. F. ROC curve was plotted for MPI score categories against the number of mortality using Medcalc statistical software. DeLong et al method and binomial exact with 95% confidence interval regarding AUC was performed for statistical significance, where $p < 0.001$. G. ROC curve was plotted for MPI score categories against morbidity (complications) using Medcalc statistical software. DeLong et al. method and binomial exact with 95% confidence interval regarding AUC was performed for statistical significance, where $p < 0.001$.

We found significant AUC providing distinction and specificity of prediction between various MPI scores. Surprisingly, mortality rates of in-house study was low (5.5%) as compared to other states of India. Given the overall mortality for secondary peritonitis and associated complications in the Asian population, studies range from ~9-20% in comparison to Western population (~25-40%) which might indicate a genetic and environmental influence (28,29,31). Other groups had reported higher mortality in Indian patients with secondary peritonitis (44). However, the burden of infectious diseases like typhoid, tuberculosis alongside poor patient management should be taken into account while estimating mortality and morbidity in Indian patients. Overall, our study suggests MPI based scoring system is efficient in predicting outcomes and categorizing patients for better management and care.

CONCLUSION

In spite of improved diagnostic modalities and treatment regime, secondary peritonitis and subsequent sepsis-related mortality accounts for ~16 to 34% death in patients worldwide (2,28,29). Our study results indicate MPI parameters like age and sex follow similar trends with the western population regarding mortality. Whereas other parameters like source/site of perforation in most cases were restricted to the upper alimentary canal owing to higher enteric infections as compared to the distal intestinal parts in western population. Mortality rates were significantly higher (>20%) in studies due to high evolution time (>24 hours), diffused nature of peritonitis with associated infection in exudate cultures and comorbidity parameters like sepsis and organ failure. One of the major reasons for such association might be due to delayed presentation, under-developed health care system, unavailability of critical care and delay in early intervention resulting in development of sepsis, SIRS (systemic inflammatory response syndrome) and MODS (multi organ dysfunction syndrome) (29,32-35). From our MPI based studies, we speculate the risk category of peritonitis patients with MPI score as <21 (low risk), 21-29 (moderate risk) and >29 (high risk) as a better assessment parameter to predict treatment modalities and outcomes. We found that age and sex dependent increment in MPI score is often guided by the inclusion of the patients in the studies. Perforation site has a strong association with the severity of secondary peritonitis and development of complications. Gastroduodenal, ileal, appendicular perforations are the most common among all studies. Complications including sepsis, septicaemia and organ failure are always associated with the evolution time of the disease.

Ethics Committee Approval: Ethics approval [No: A/206/REB-Comm (SP)/RIMS/2015/472/90/2018] was obtained from Research Ethics Board Regional Institute of Medical Sciences Imphal before the commencement of the study. Signed informed consents were taken from all participants. Privacy of the participants was maintained. No organ/sample were procured from any prisoners. Apart from the in-house study data, data for all studies were curated from a published work so requirement of ethics approval for published studies was revoked.

Peer-review: Externally peer-reviewed.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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ORJİNAL ÇALIŞMA-ÖZET

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Coğrafi olarak farklı Hintli hastalarda Mannheim peritonit indeksi kullanılarak sekonder peritonit sonuçları üzerine karşılaştırmalı analitik bir çalışma

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ÖZET

Giriş ve Amaç: Sekonder peritonit, sindirim kanalının delinmesine bağlı olarak periton boşluğunun enfekte olmasıdır. Mannheim peritonit indeksi (MPI), bir cerrahın peritonitli hastanın sağkalım sonucunu tahmin etmesini sağlayan prognostik bir skorlama sistemidir. Artan MPI skorları kötü prognoz ve mortaliteyle ilişkilidir. Bu çalışmanın amacı Mannheim peritonit indeksinin prognozu tahmin etmede bir araç olarak rolünü ve Hindistan alt popülasyonlarında sekonder peritonitli hastaların yaşamları üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Hindistan'ın kuzeydoğusundaki bölgesel bir hastanede sekonder peritonit tanısıyla hastane verilerine dayanan bir çalışma yürütülmüştür. Karşılaştırmalı analiz için Hindistan'ın coğrafi olarak farklı 10 bölgesinden veriler kullanılmıştır.

Bulgular: Hastaların çoğunda genç (<50 yaş) erkeklerin baskın olduğunu gözlemledik. Perforasyon bölgeleri, çoğunluğu gastroduodenal olmak üzere üst sindirim kanalında sık görülmekteydi. Çalışma merkezindeki ölüm oranı birçok Hint çalışmasına kıyasla düşüktü (%5,5), bu da Kuzeydoğu Hint alt popülasyonunda hastalığın sonucunu belirleyebilecek genetik ve çevresel faktörlere bağlı bir olası farka işaret etmektedir.

Sonuç: Mortalite ve morbiditeyi azaltmak için MPI > 29 olan hastalarda agresif resüsitasyon ve hastaların izlenmesi, geniş spektrumlu antibiyotiklerin başlanması ve yoğun bakım desteği düşünülmelidir.

Anahtar Kelimeler: Sekonder peritonit, Mannheim peritonit indeksi, enfeksiyon, mortalite

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