

Type of Manuscript: Original Article

Sepsis, a Common Endpoint to Even Non-Infectious Comorbidities, A Single Center Study on 49,107 Patients, at a Tertiary Care Center in India

Dhaval Dalal¹, Girish Rathod², Kamalpriya Thiyagarajan³, Namrata Britto⁴, Veda Devakumar⁵,
Vijaykumar Gawali⁶

¹Professor, Internal Medicine, Department of Internal Medicine, Consultant Internal medicine, ²Head of Orthopedic Department, Consultant Orthopaedician, Bhaktivedanta Hospital and Research Institute, Thane, Maharashtra, India, Bhaktivedanta Hospital and Research Institute, ³Professor, Gynaecology and Obstetrics, DGO, Consultant Obstetrician & Gynaecologist, Medical Research Department, Bhaktivedanta Hospital and Research Institute, ⁴Research Scholar, MSc. Biological Sciences, Department of Biological Sciences, Sunandan Divatia School of Science, NMIMS, Deemed to be University, Thane, Maharashtra, India, ⁵Research Scholar, Department of Medical Research, Bhaktivedanta Hospital and Research Institute, Bhaktivedanta swami Marg, sector 6, Srishti complex, Mira Road, Thane: 401107, Maharashtra, India

Abstract

Background & Objectives- Sepsis, is caused by dysregulated host response that leads to multiple organ dysfunction. Complications of sepsis being so grave, it becomes important to address it in a community setting as sepsis always presents itself as a reason for clinical deterioration of preventable and common diseases.

Methods- Analysis of in-patient records of 49,107 at a tertiary care centre in India were analysed from years 2016-2020, to study correlation of sepsis with various comorbidities such as Diabetes, Hypertension, Coronary artery disease, Cerebrovascular accident and Thyroid; and also, to study the death toll occurring due to sepsis.

Results- Sepsis has a higher prevalence in the vulnerable age groups that is > 60 years followed by < 20 years of age. Sepsis is observed more in males (56.32%) than females (43.68%). Sepsis was found to have a statistically significant association ($P < 0.0001$) with Diabetes, Hypertension, Coronary artery disease and cerebrovascular accident. 38% of total deaths that occurred in the hospital were due to sepsis. 68.9% of patients who died due to sepsis were ICU cases.

Interpretations & Conclusions- Septic patients are 9 times more prone to death than non-septic patients in an Intensive care unit. There is no statistically significant association between thyroid disorder and sepsis ($P = 0.38$). Generally, a researcher would expect diabetes to be a major contributor to sepsis, however our paper reports 70% of total septic cases to be non-diabetic ones. Sepsis itself is caused due to microbial infections but the comorbidities contributing to its prevalence are non-infectious in nature.

Keywords- Cerebrovascular accident, Coronary artery disease, Diabetes, Hypertension, infection, sepsis, septic shock, Thyroid.

Corresponding Author:

Dr. Girish Rathod

Email: drgirishrathod@gmail.com,

Phone address: +91 9321996804

Introduction

Sepsis is an increasing cause of morbidity and mortality worldwide. ⁽¹⁾ Sepsis, also known

as septicemia, occurs due to bacterial, fungal and viral infections. It could also be life threatening if not treated well. ⁽²⁾ Its symptoms include low blood pressure, difficulty in breathing, chills, mental confusion, skin discoloration, organ dysfunction. In non-medical terms, sepsis is referred to as blood poisoning. Sepsis itself isn't contagious, but its causative pathogens may be one. Sepsis consists of three stages: stage one being sepsis itself, stage two as severe sepsis and stage three being septic shock; this stage is characterized by an escalated microbiological burden. ⁽³⁾ This increase in the microbiological burden, results in the experience of failure of various organs that often leads to death of an individual. Thus, septic shock is known to be one of the most common causes of death worldwide. The leading pathogens involved in neonatal and maternal septic infections include Group B streptococcus and *Escherichia coli*. ⁽⁴⁾ The prevalence of sepsis has been high in India too. In January 2020 the results of a Global study published in *The Lancet* revealed that India stands second highest in death caused due to sepsis in South Asia ⁽⁵⁾. Sepsis does remain the leading cause of death in Intensive care units, till date. ^(6, 7, 8, 9)

In this study we aim to understand the association of septicemia with comorbidities such as diabetes, hypertension, coronary artery disease, cerebrovascular disease and thyroid.

Materials and Method

Post institutional ethics committee approval, the data records of all patients admitted in the hospital from year 2016 to 2020 was retrieved from the Medical records department. Parameters like age group, gender, no. of deaths, association of sepsis with comorbidities such as diabetes mellitus, hypertension, coronary artery disease, cerebrovascular accident and thyroid were studied as shown below in figure 1. A total data of 49,107 patients were analysed for this study. Statistical analysis of the data was performed using SPSS software.

Results

The obvious risk factors for sepsis is infection. The infection could be bacterial, fungal or viral too. The

main treatment for sepsis is antibiotics especially via IV. But if the condition becomes severe then severe sepsis is termed as a time critical condition which increases the chances of death of an individual for every delayed response during treatment. But what could be a way to fight against sepsis? The only way is by understanding factors contributing to/leading to sepsis and providing in-time treatment for it.

Subsequent to analysis of data it was observed that Sepsis has a rising trend from 2016-2020. The following are the percentages- 1.74%, 1.81%, 2.08%, 2.07%, 2.86%, 2.1% for 2016, 2017, 2018, 2019, 2020 respectively.

Gender wise, males are more prone to sepsis and age wise aged people (above 60 years) are more prone to sepsis. Sepsis was found to have statistically significant association ($P < 0.0001$) with diabetes, hypertension, coronary artery disease and cerebrovascular accident; implying that existence of sepsis with these comorbidities could prove to be fatal for a patient. From the total deaths that occurred in the hospital, 38% deaths were due to sepsis. Death due to sepsis was highly found in ICU patients (68.9%) as compared to ward patients (31.09%). Among all ICU cases in the hospital, the number of patients who died due to sepsis were 9 times more than those who died without sepsis indicating the severity of the case.

Discussion

Sepsis, a life-threatening condition of the body that occurs due to microbial infections, eventuates to organ dysfunction in humans. No matter what the origin or cause of infection, sepsis is a result of a mishandled immune response in which inflammation has spread to various organs of the body. ⁽¹⁰⁾ If left untreated, it could lead to stage three- septic shock that could result in death of a patient. Despite of best possible treatments, around 50% of sepsis survivors suffer with post-sepsis syndrome (PSS). PSS includes long term effects such as: damaged organs, insomnia, lowered cognitive functioning, fatigue, disabled muscle and joint pain and much more. ^(11, 12) In short, sepsis does have a huge impact on human lives even if treated or left untreated. Hence it

is incumbent to address this issue and understand what other comorbidities could possibly contribute to this condition; helping us to gain more insights for better treatment of a patient. The discussion part is categorized under the following nine sections.

1. Age

In multiple previous studies, it has been observed that people of age 60 years and above are highly prone to sepsis and mortality due to sepsis. This could be due to the fact that in elderly people, the White Blood Cell counts are slightly low as compared to other age groups, but a rise in the total WBC count is observed during sepsis or an acute infection; some reports do suggest that this increased WBC count could result as a predisposing factor to bacteremia. Thus, contributing to the condition of septicemia. ⁽¹³⁾ In this study, age groups of 0-20 years, 21-40 years, 41-60 years and 61 & above were observed for having the condition of sepsis and it was observed that the age group of 61 and above (i.e., elderly people) are highly prone to sepsis; followed by younger children (0-20 years). It can thus be concluded that people in the vulnerable age group are found to be more prone to sepsis. In this study, significant association between age group 61 & above and sepsis has been observed. ($P < 0.0001$)

2. Gender

Many studies reveal that males are more prone to sepsis as compared to females. Mortality due to sepsis are higher in males than females. This may be due to the fact that, women exhibit stronger immune responses as compared to males which could favor the clearance of pathogens from the body and could contribute to immune mediated pathologies such as in inflammatory diseases and autoimmune diseases. ⁽¹⁴⁾ In this study, 56.32% males and 43.68% females were found to have septicemia.

3. Deaths due to sepsis

Severe sepsis is a common occurrence in India. In

a study conducted in 2017 with 4711 patients, it was found that, death occurring due to sepsis was 56.1%. It also inferred that most infections were stemmed from the respiratory tract. ⁽¹⁵⁾ In our study there is an increase in the trend of death along with sepsis. Stage 3 septic shock is highly lethal as it often leads to organ failure especially when the pathogen involved in the infection is multi drug resistant. Worldwide mortality due to sepsis is at an all-time high at 85.0% according to WHO. ⁽⁴⁾ Hence it is imperative to manage sepsis in a hospital setting. In our study it was observed that in the presence of sepsis, the mortality rate was observed to be higher as compared to patients without sepsis. We analysed all death cases (total 430 deaths) from 49,107 in-patient records. Sepsis does prove to contribute to cases becoming severe as 38.13% of total deaths that occurred in the hospital from 2016-2020 was due to sepsis.

4. Sepsis with Diabetes mellitus

It is believed that diabetic patients are commonly prone to sepsis, this could be as sepsis causes upregulation of many hormones such as vasopressin, cortisol, insulin and IGF-I. ⁽¹⁶⁾ Diabetic patients have an increased risk of developing sepsis that constitutes up to approximately 20 - 22%. ⁽¹⁷⁾ This is because diabetes does cause a reduction in a cell's immune function causing immune deficiency; this leads to the display of minimal bacterial clearance by the patients with increased risks to infections and higher mortality rates. ⁽⁵⁾ In this study, a significant association ($P < 0.0001$) was observed between diabetes and sepsis suggesting that the case of a diabetic patient could turn out to be fatal if sepsis is present. Epidemiology and outcome of stage 2 and 3 of sepsis in a South Indian tertiary care hospital conducted in 2017 suggested that diabetes mellitus was the major comorbidity prevalent in septic patients, that was found to be around 51.2% ⁽¹⁸⁾; whereas in our study it was found to be 29.96%. Prevalence of sepsis along with diabetes is observed in Table I.

Table I: Prevalence of sepsis with diabetes

	diabetic	non-diabetic	Total
septic	308 (29.96%)	720 (70.03%)	1028 (100%)
non-septic	7609 (15.82%)	40470 (84.17%)	48079 (100%)
Total	7917 (16.12%)	41190 (83.87%)	49107 (100%)

(Chi-square = 147.665, P<0.0001)

5. Sepsis with Hypertension

A study conducted in 2014 showed that both systolic and diastolic blood pressure values are higher in patients with sepsis. ⁽¹⁹⁾ This can be attributed to the fact that sepsis does endocrinological changes which often leads to progression of this disease. A case report published in May 2014 suggested the prospective study that acute arterial hypertension must be researched in a sepsis

setting. ⁽²⁰⁾ As explained earlier that sepsis is caused due to prevailing bacterial infections, these bacteria produce toxins; and the untreated toxins could lead to the damage of tiny blood vessels, causing them to leak out of the tissues they are surrounded by. This could thus affect a person's blood pumping ability and thus causing low blood pressure. ⁽²¹⁾ In our study that analyzes the cases of 49,107 patients, there was a statistically significant association found between sepsis and hypertension (P<0.0001). Results are documented in Table II.

Table II: Prevalence of sepsis with hypertension

	hypertensive	non-hypertensive	Total
septic	290 (28.21%)	738 (71.78%)	1028 (100%)
non-septic	8094 (16.83%)	39985 (83.16%)	48079 (100%)
Total	8384 (17.07%)	40723 (82.92%)	49107 (100%)

(Chi-square = 91.186, P<0.0001)

6. Sepsis with Coronary artery disease

Many studies show that having sepsis does increase the risk of cardiac dysfunction, this is because as sepsis worsens, the flow of blood to all the vital organs of our body gets impeded. As sepsis may cause abnormal blood clotting that would lead to damage in tissues and blood vessels of all vital organs such as heart, brain, kidneys, etc. Sepsis induced systemic inflammation could also be a factor affecting the cardiovascular system. It has been

observed that most people do survive or recover from mild sepsis but the mortality rate for septic shock still remains as high as 40%. ⁽²²⁾ In this paper, a statistically significant association (P<0.0001) was found to be present between sepsis and Coronary artery disease as shown in Table III, proposing that septic patients are more prone to cardiac dysfunction that could possibly lead to organ failure.

Table III: Prevalence of sepsis with Coronary artery disease

	coronary artery disease	non- coronary artery disease	Total
septic	168 (16.34%)	860 (83.65%)	1028 (100%)
non-septic	5593 (11.63%)	42486 (88.36%)	48079 (100%)
Total	5761 (11.73%)	43346 (88.26%)	49107 (100%)

(Chi-square = 21.105, P<0.0001)

7. Sepsis with Cerebrovascular accident

Sepsis has also been a concern in patients who have suffered a stroke, due to the immunosuppressed environment and their susceptibility to infections. Studies suggest that infections prior to stroke are not associated with stroke severity suggesting sepsis not to be a predecessor of stroke. ⁽²³⁾ Septic shock is often associated with acute brain dysfunction as sepsis causes inflammatory and non-inflammatory processes that leads to alterations in various vulnerable parts of the brain. ⁽²⁴⁾ Table IV tells us that there was a significant association (P<0.0001) observed between sepsis and Cerebrovascular accident which tells us that stage 3 sepsis (septic shock) could lead to brain damage and further systemic failures.

Table IV: Prevalence of sepsis with Cerebrovascular accident

	cerebrovascular accident	non- cerebrovascular accident	Total
septic	64 (6.22%)	964 (93.77%)	1028 (100%)
non-septic	1120 (2.32%)	46959 (97.67%)	48079 (100%)
Total	1184 (2.41%)	47923 (97.58%)	49107 (100%)

(Chi-square = 63.289, P<0.0001)

8. Sepsis with Thyroid

Studies have revealed that sepsis is often accompanied with T₃ syndrome that is caused due to thyroid dysfunction. ⁽²⁵⁾ Sepsis causes downregulation of hormones such as T₃, TSH, Testosterone and estrogen. In an experimental study conducted to understand the role of thyroid hormone in sepsis, it was shown that septic

rats showed lower mortality rates when supplemented with the thyroid hormone. ⁽²⁶⁾ It is a known fact that during illnesses, the body does show reduction in levels of the thyroid hormone. Hence one may consider that sepsis has a significant association with thyroid but in our paper, no statistically significant association was observed between sepsis and thyroid (P=0.38). Results for the same are documented in Table V.

Table V: Prevalence of sepsis with Thyroid

	thyroid	non-thyroid	Total
septic	29 (2.82%)	999 (97.17%)	1028 (100%)
non-septic	1133 (2.35%)	46946 (97.64%)	48079 (100%)
Total	1162 (2.36%)	47945 (97.63%)	49107 (100%)

(Chi-square = 0.750, P=0.3866)

9. Sepsis: a threat to ICU patients

When total deaths in the ICU were analysed, sepsis contributed to 38%. When deaths in septic population was compared with non-septic population in an ICU setting it was observed that 17.33% deaths occurred in septic population and 2.21% deaths occurred in non-septic population. It can thus be inferred that a patient with sepsis is 9 times more prone to death as compared to the one without sepsis. A study conducted in 2016 of around 4209 patients from 124 ICUs across India reported 18.1% mortality rate of septic ICU patients. (27, 28) A recent study also revealed that severe sepsis is common to ICU patients in India (15) implying that mortality rates of septic patients are higher in ICU.

Conclusion

Septic cases analysis in a nutshell - The total septic population of the hospital from 2016-2020 was analysed to study the co-prevalence of septic deaths and non-death cases with various comorbidities. The results obtained in this study suggests that septicemia, which is an infectious disease is prevalent in even those patients with comorbidities that are non-infectious in nature.

Source(s) of Funding: The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethical Clearance: Obtained

Conflicting Interest (If present, give more details):

The authors do not have any conflict of interest.

Acknowledgement: Dr. Rishikesh Karpe, Ms Neha Tiwari, Pratiksha Ingale, Akshada Vartak.

References

1. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: sampling, selection, and society. *Critical Care*. 2004 Aug;8(4):1-5.
2. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Chest*. 1992 Jun 1;101(6):1644-55.
3. Brun-Buisson C, Doyon F, Carlet J, Dellamonica P, Gouin F, Lepoutre A, Mercier JC, Offenstadt G, Régnier B. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults: a multicenter prospective study in intensive care units. *Jama*. 1995 Sep 27;274(12):968-74.
4. Sepsis [Internet]. *Who.int*. 2020 [Aug 26]. Available from: <https://www.who.int/news-room/fact-sheets/detail/sepsis>
5. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, Colombara DV, Ikuta KS, Kissoon N, Finfer S, Fleischmann-Struzek C. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet*. 2020 Jan 18;395(10219):200-11.
6. Frydrych LM, Fattahi F, He K, Ward PA, Delano MJ. Diabetes and sepsis: risk, recurrence, and

- ruination. *Frontiers in endocrinology*. 2017 Oct 30;8:271.
7. Agarwal R, Gupta D, Ray P, Aggarwal AN, Jindal SK. Epidemiology, risk factors and outcome of nosocomial infections in a Respiratory Intensive Care Unit in North India. *Journal of Infection*. 2006 Aug 1;53(2):98-105.
 8. Ghanshani R, Gupta R, Gupta BS, Kalra S, Khedar RS, Sood S. Epidemiological study of prevalence, determinants, and outcomes of infections in medical ICU at a tertiary care hospital in India. *Lung India: Official Organ of Indian Chest Society*. 2015 Sep;32(5):441.
 9. Pradhan NP, Bhat SM, Ghadage DP. Nosocomial infections in the medical ICU: a retrospective study highlighting their prevalence, microbiological profile and impact on ICU stay and mortality. *J Assoc Physicians India*. 2014 Oct 1;62(10):18-21.
 10. Parry N. The death toll of sepsis in India [Internet]. *Health Issues India*. 2021. Available from: <https://www.healthissuesindia.com/2018/09/13/the-death-toll-of-sepsis-in-india/>
 11. Sepsis: Symptoms, Causes, Treatment, Risks & More [Internet]. *Healthline*. 2021. Available from: <https://www.healthline.com/health/sepsis#recovery>
 12. Post-Sepsis Syndrome | Sepsis Alliance [Internet]. *Sepsis Alliance*. 2021. Available from: <https://www.sepsis.org/sepsis-basics/post-sepsis-syndrome/>
 13. Aminzadeh Z, Parsa E. Relationship between age and peripheral white blood cell count in patients with sepsis. *International journal of preventive medicine*. 2011 Oct;2(4):238.
 14. [Internet]. 2021. Available from: <https://www.frontiersin.org/research-topics/6645/sex-hormones-and-gender-differences-in-immune-responses>.
 15. Chatterjee S, Bhattacharya M, Todi SK. Epidemiology of adult-population sepsis in India: a single center 5 year experience. *Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine*. 2017 Sep;21(9):573.
 16. Widmer A, Schuetz P. Endocrine dysfunction during sepsis—are changes in hormone levels a physiological adaptation or a therapeutic target?. *Journal of Laboratory and Precision Medicine*. 2018;3:61-61.
 17. Assiut University Hospital - Full Text View - ClinicalTrials.gov [Internet]. *Clinicaltrials.gov*. 2019. Available from: <https://clinicaltrials.gov/ct2/show/NCT04015752>
 18. Pandey NR, Bian YY, Shou ST. Significance of blood pressure variability in patients with sepsis. *World journal of emergency medicine*. 2014;5(1):42.
 19. Babu M, Menon VP, Devi UP. Epidemiology and outcome among severe sepsis and septic shock patients in a South Indian tertiary care hospital. *Int J Pharm Pharm Sci*. 2017;9(5):256-9.
 20. Saleh M. Sepsis-related hypertensive response: friend or foe?. *Case Reports*. 2014;2014(may22 1):bcr2014204610-bcr2014204610.
 21. Septic shock symptoms and treatment [Internet]. *Nhsinform.scot*. 2021. Available from: <https://www.nhsinform.scot/illnesses-and-conditions/blood-and-lymph/septic-shock>
 22. Sepsis - Symptoms and causes [Internet]. *Mayo Clinic*. 2021. Available from: <https://www.mayoclinic.org/diseases-conditions/sepsis/symptoms-causes/syc-20351214>
 23. Berger B, Gumbinger C, Steiner T, Sykora M. Epidemiologic features, risk factors, and outcome of sepsis in stroke patients treated on a neurologic intensive care unit. *Journal of critical care*. 2014 Apr 1;29(2):241-8.
 24. Sonnevile R, Verdonk F, Rauturier C, Klein IF, Wolff M, Annane D, Chretien F, Sharshar T. Understanding brain dysfunction in sepsis. *Annals of intensive care*. 2013 Dec;3(1):1-1.
 25. Luo B, Yu Z, Li Y. Thyroid hormone disorders and sepsis. *Bio-medical materials and engineering*. 2017 Jan 1;28(s1):S237-41.
 26. Inan M, Koyuncu A, Aydin C, Turan M, Gokgoz S, Sen M. Thyroid hormone supplementation in sepsis: an experimental study. *Surgery today*. 2003 Jan;33(1):24-9.
 27. Singh V, Todi S, Sahu S, Jani C, Kulkarni A, Samaddar D et al. Intensive Care in India: The Indian Intensive Care Case Mix and Practice Patterns Study. *Indian Journal of Critical Care*

- Medicine. 2016;20(4):216-225.
28. Polat G, Ugan RA, Cadirci E, Halici Z. Sepsis ve septik şok: Mevcut tedavi stratejileri ve yeni yaklaşımlar. *Eurasian J. Med.*. 2017;49:53-8.