Original Article

Potential role of mitochondrial uncoupling protein 2 as a biomarker in patients with sepsis and septic shock: A prospective observational study

Address for correspondence:
Dr. Roopa Sachidananda, Department of Anaesthesiology, Karnataka Institute of Medical Sciences, Hubli - 580 021, Karnataka, India.
E-mail: roopasac@gmail.com

Submitted: 07-Dec-2023
Revised: 14-Apr-2024
Accepted: 04-May-2024
Published: 02-Jul-2024

Access this article online

Website: https://journals.lww.com/ijaweb

DOI: 10.4103/ija.ija_1181_23

Quick response code

Roopa Sachidananda, Vikram Kemmannu Bhat[1], Mahantesh Kurjogi[2], Gulam Nabi L. Vanti[2], Madhura Kayara

Departments of Anaesthesia, [1]ENT and [2]Multi-Disciplinary Research Unit, Karnataka Institute of Medical Sciences, Hubli, Karnataka, India

ABSTRACT

Background and Aims: Early diagnosis of sepsis is crucial. The primary objective of this study was to explore the role of uncoupling protein 2 (UCP2) in diagnosing sepsis and septic shock. **Methods:** This prospective observational study was conducted over 19 months. All adult patients aged more than 18 years with a diagnosis of sepsis or septic shock based on quick sequential organ failure assessment (qSOFA) score were enroled. Blood was drawn for procalcitonin (PCT) and UCP2 on days 0, 3, 7 and 28. Blood samples from 50 healthy volunteers were used as controls. An electrochemiluminescence test was done for PCT. A quantitative enzyme-linked immune sorbent assay was used for UCP2. The Chi-square test was used for qualitative variables and the independent *t*-test for quantitative variables. The receiver operator characteristic curve was used to evaluate the diagnostic efficacy of UCP2. **Results:** A total of 128 subjects were included in the study. Out of these, 78 patients (qSOFA score ≥2) were subcategorised into the infection group, sepsis or septic shock group based on the PCT levels. The UCP2 levels in the infection, sepsis or septic shock group were significantly higher than in the control group ($P > 0.001$). The UCP2 levels correlated with PCT on admission, day 3 and day 7. **Conclusion:** The UCP2 levels were significantly higher in sepsis and septic shock groups compared to controls and hence could be a potential diagnostic biomarker of sepsis.

Keywords: Biomarkers, procalcitonin, sepsis, shock, uncoupling protein 2, qSOFA

INTRODUCTION

Sepsis is one of the most prevalent causes of morbidity and mortality in the intensive care unit (ICU).[1,2] Various biomarkers have been evaluated to diagnose and predict the prognosis of sepsis and assess the response to therapeutic intervention, but these are still debatable. Procalcitonin (PCT) continues to be a reliable biomarker in sepsis. PCT is an amino acid precursor of calcitonin synthesised by thyroid cells and secreted by various other cells, including immune cells, during the proinflammatory phase of sepsis. The biomarkers increase within 4 h from the start of the innate immunity cascade, peaking within 6–8 h.[3]

The pathophysiology of sepsis is complex due to mitochondrial injury, resulting in structural and functional changes.[4] Uncoupling protein 2 (UCP2) is present on the mitochondrial inner membrane.[5] Various studies have shown the involvement of UCP2 in the regulation of inflammation, oxidative stress, maintenance of mitochondrial membrane potential and energy production, which may be related to the pathophysiology of sepsis. Since all cells have mitochondria, they express UCP2 in sepsis. Hence,

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Sachidananda R, Bhat VK, Kurjogi M, Vanti GN, Kayara M. Potential role of mitochondrial uncoupling protein 2 as a biomarker in patients with sepsis and septic shock: A prospective observational study. Indian J Anaesth 2024;68:718-24.

UCP2 expression could be used as a biomarker in the early diagnosis and prognosis of sepsis.[6]

While the search for highly specific and sensitive biomarkers for early diagnosis, prognosis and treatment of sepsis continues, UCP2 may play an important role. However, the role of UCP2 in sepsis remains unclear. Hence, we hypothesised that UCP2 has the same diagnostic value as PCT in this study. The primary objective was to explore the role of UCP2 in diagnosing sepsis and septic shock. The secondary objective was to compare it with biomarker PCT.

METHODS

This prospective observational study was conducted in a tertiary hospital between December 2021 and July 2023. Institute Ethics Committee approval was obtained for the research (vide approval number KIMS: ETHICSCOMM.55,2020-2021 dated 19.05.2021), and the study was registered in the Clinical Trials Registry-India (vide registration number CTRI/2021/08/0365051, www.ctri.nic.in). The study followed the Declaration of Helsinki, 2013 and was conducted in accordance with the Good Clinical Practice guidelines. Written informed consent was obtained for participation in the study and using data for research and educational purposes. Patients of age more than 18 years, admitted to the surgical intensive care unit (SICU) or medical intensive care unit (MICU) with a diagnosis of sepsis or septic shock based on quick sequential organ failure assessment (qSOFA) score, were enroled in the study. Patients with primary or secondary immunodeficiency syndrome, those on treatment with corticosteroids or immune modulators in the previous six months, those with burns, those with a history of blood transfusion six months before admission and pregnant women were all excluded from the study.

Sequential organ failure assessment (SOFA) scores were assessed on days 0, 3, 7 and 28. Blood was drawn for PCT and UCP2 on days 0, 3, 7 and 28. Blood sample was drawn from 50 healthy volunteers as controls for serum UCP2 levels. An electrochemiluminescence test was performed for PCT (fully automated analyser, Abbot ARCHITECT Ci4100; Abbott Park, IL, USA). Range more than 0.5 ng/ml was suggestive of sepsis/septic shock. A quantitative enzyme-linked immune sorbent assay (ELISA) was used for the UCP2 protein (UCP2 GENLISA™ ELISA REF: KBH2064; Krishgen Biosystems, Mumbai, India).

The principle of assay employed the sandwich ELISA technique. Monoclonal antibodies were pre-coated onto microwells. Samples (plasma) and standards were pipetted into microwells, and the immobilised antibodies bound the UCP2 present. A biotin-labelled antibody was added, and then streptavidin–horseradish peroxidase was added, and the complex formed was incubated. After washing microwells to remove any non-specific binding, the substrate solution (tetramethylbenzidine) was added to the wells. The colour developed in proportion to the amount of UCP2 bound in the initial step. Finally, the colour development was stopped by adding a stop solution. Absorbance was measured at 450 nm (Biorad).

The primary outcome was to determine the diagnostic role of UCP2 as a biomarker in sepsis and septic shock against controls who were healthy volunteers. The secondary outcome was to compare sensitivity and specificity with known biomarker PCT.

The sample size estimated between two proportions of expression of reverse transcription-polymerase chain reaction analysis of UCP2 mRNA level in blood cells in patients with sepsis and healthy individuals, according to the study done by Jiang *et al.*,[6] was 79% expression in sepsis patients and 8% in healthy individuals. Taking 10% as the absolute precision and a 90% confidence interval (CI), the sample size in each group was estimated to be 65. Data were entered in Statistical Package for Social Sciences software (version 17.0; IBM, Chicago, IL, USA). The Chi-square test was used for qualitative variables such as gender and comorbid illnesses like diabetes mellitus and hypertension, and the independent *t*-test was used for quantitative variables such as heart rate, mean arterial pressure, ICU mortality and blood investigations. The receiver operator characteristic (ROC) curve was used to evaluate the diagnostic efficacy of the biomarkers UCP2 and PCT. The Pearson correlation coefficient method was used for correlation analysis. The area under the ROC curve was used to predict the accuracy of septic shock by UCP2. A *P*-value of <0.05 was considered statistically significant.

RESULTS

A total of 128 patients were included in the study. Of these, 78 patients with obvious or suspected infection (who had qSOFA score ≥ 2) were subcategorised into the infection group, sepsis group and septic shock group based on sepsis 3 diagnostic criteria for sepsis (PCT value >0.5 ng/ml suggestive of sepsis/septic

shock as per blood investigation). Five patients were excluded from the study as they were unwilling to give the blood sample [Figure 1]. Patients' demographic data at admission is shown in Table 1.

Thirty-five males and nine females were in the sepsis group, while 16 males and three females were in the septic shock group. The mean (standard deviation [SD]) age in the sepsis group was 49.68 (15.18) years, and in the septic shock group was 58.05 (15.12) years ($P = 0.049$). The results of investigations on admission are presented in Table 2.

The UCP2 level in the control group was 75.4 ng/ml. The UCP2 levels in the infection, sepsis and septic shock groups were significantly higher than the control group [area under the curve (AUC): 0.80 (95% CI: 0.772, 0.878), $P < 0.001$] [Figure 2]. The relative risk was 2.60 [95% CI: 1.68, 4.03].

UCP2 levels of more than 88.4 ng/ml suggested sepsis or septic shock. The relative risk was 1.063 [95% CI: 0.82, 1.38]. The sensitivity of the test was 73 [95% CI: 60.3, 80.4], specificity was 33.3 [95% CI: 11.8, 61.6], positive predictive value was 82.1 [95% CI: 69.6, 91.1], and the negative predictive value was 22.7 [95% CI: 7.8, 45.4]. The septic shock group had higher levels of UCP2 with a mean (SD) value of 129.21 (45.05) ng/ml than the sepsis group [107.26 (44.20) ng/ml] ($P = 0.077$). The ROC curve of the accuracy of predicting

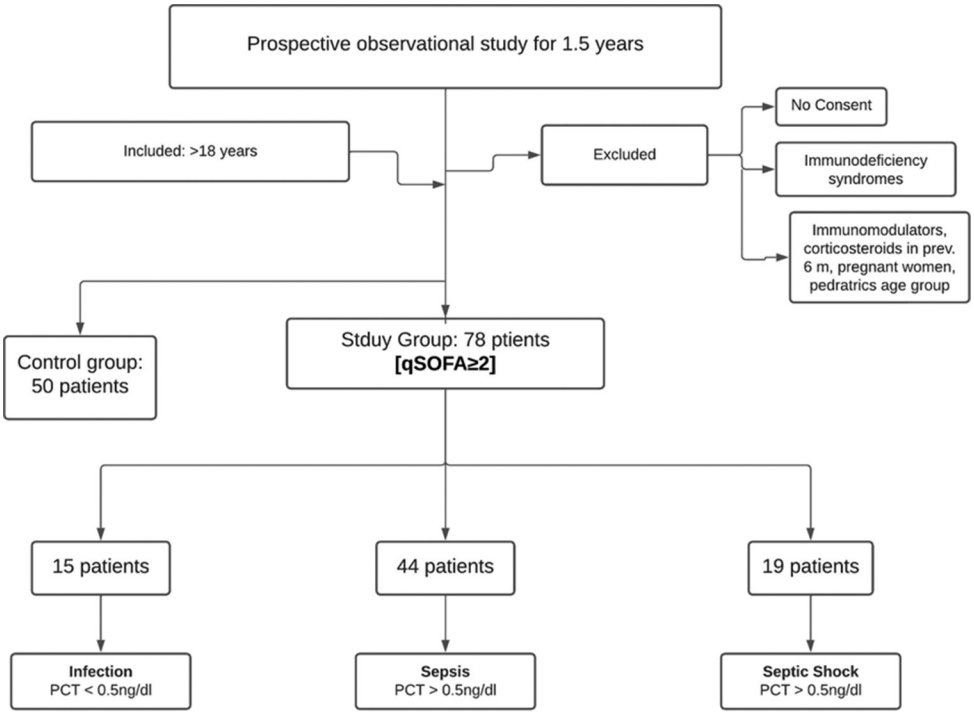

Figure 1: Flowchart of screening and composition of the study population. PCT = Procalcitonin, qSOFA = Quick sequential organ failure assessment

Table 1: Demographic data of the study participants at the time of admission

Variable	Control group (*n*=50)	Infection (*n*=15)	Sepsis + septic shock (*n*=63)	*P*
Age (years), mean (SD) (95% CI)	37.9 (14.9) [33.77–48.03]	52.0 (20.6) [41.575–62.425]	52.2 (15.5) [48.373–56.027]	<0.001
Gender (male/female), *n*	31/19	10/5	52/11	0.035
Diabetes mellitus, *n*	6	5	19	0.030
Hypertension, *n*	1	3	8	0.037
qSOFA, median (IQR)		2 (2–3)	3 (2–3)	0.006
Heart rate (bpm), mean (SD) (95% CI)		106.3 (16.5) [97.9, 114.6]	100.7 (23.2) [94.9, 106.4]	0.295
MAP (mmHg), mean (SD) (95% CI)		81.8 (10.4) [76.5, 87.0]	79.8 (12.9) [76.6, 82.9]	0.532
Discharged from hospital, mean (SD) (95% CI)		11 (84.6) [31.8, –53.8]	32 (61.5) (16.8, 47.1)	0.116
ICU mortality, mean (SD) (95% CI)		2 (15.4) [5.79, 9.79]	20 (38.5) [10.49, 29.50]	0.116
Number of hospital days, mean (SD) (95% CI)		10.3 (7.1) [6.70, 13.89]	10.0 (7) [8.27, 11.73]	0.805

Data expressed as mean (standard deviation) [95% confidence interval]/median (IQR). bpm=beats per minute, ICU=intensive care unit, IQR=interquartile range, MAP=mean arterial pressure, qSOFA=quick sequential organ failure assessment, SD=standard deviation, CI=confidence interval, n=number of patients

Table 2: Investigations at the time of admission (day 0)

Variable	Normal value	Infection (*n*=15)	Sepsis + septic shock (*n*=63)	*P*
Haemoglobin (g/dl), mean (SD) (95% CI)	11–16	11 (2) [9.98, 12.01]	11 (2.6) [10.35, 11.64]	0.902
Platelet count (cells/mm^3), mean (SD) (95% CI)	1.5–4.5	3.7 (1.4) [2.99, 4.40]	2.6 (1.7) [2.18, 3.02]	0.014
Total count (cells/mm^3), median (IQR)	4500–11,500	10,750 (7000–15,800)	11,700 (8000–16,700)	0.536
Serum creatinine (mg/dl), mean (SD) (95% CI)	0.7–1.3	1.1 (0.3) [0.94, 1.25]	1.6 (1.4) [1.25, 1.94]	0.01
Total bilirubin (mg/dl), median (IQR)	0.3–1.0	1.2 (0.9–1.2)	1.1 (0.8–1.9)	0.381
Direct bilirubin (mg/dl), mean (SD) (95% CI)	0.1–0.3	0.4 (0.4) [0.19, 0.60]	0.5 (0.6) [0.35, 0.64]	0.390
Total protein (mg), mean (SD) (95% CI)	6–8.3	5.9 (0.8) [5.49, 6.30]	5.3 (1.1) [5.02, 5.57]	0.042
Serum albumin (mg), mean (SD) (95% CI)	3.4–5.4	2.4 (0.5) [2.14, 2.65]	2.3 (0.7) [2.12, 2.47]	0.791
SGOT (U/l), median (IQR)	7–56	32.5 (23.0–41.0)	42.0 (27.0–71.0)	0.053
SGPT (U/l), median (IQR)	7–56	21.0 (19.0–40.0)	29.0 (17.0–40.0)	0.664
Alkaline phosphatase (U/l), median (IQR)	44–147	115.0 (74.0–150.0)	105.0 (76.0–161.0)	0.898
Blood glucose (mg/dl), median (IQR)	70–100	122.5 (100.0–155.0)	126.0 (101.0–178.0)	0.759
Sodium (mEq/l), mean (SD) (95% CI)	135–145	135.6 (7.4) [131.85, 139.34]	131.9 (7.4) [130.07, 133.72]	0.114
Potassium (mEq/l), mean (SD) (95% CI)	3.5–5.2	4.1 (0.9) [3.64, 4.55]	4.8 (5.7) [3.39, 6.20]	0.396
Procalcitonin (ng/ml), median (IQR)	<0.5	0.2 (0.1–0.3)	6.6 (2.6–25.6)	<0.001

Data are expressed as mean (standard deviation) [95% confidence interval]/median and IQR or *n*. IQR=interquartile range, qSOFA=quick sequential organ failure assessment, SGOT=serum glutamic oxaloacetic transaminase, SGPT=serum glutamic pyruvic transaminase, UCP2=uncoupled protein 2, SD=standard deviation, CI=confidence interval, *n*=number of patients

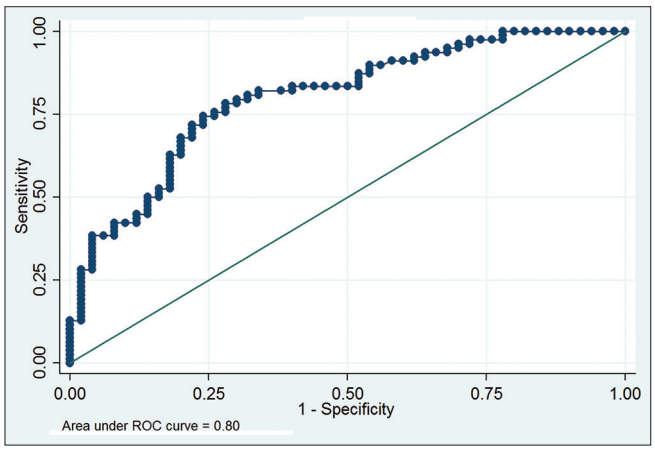

Figure 2: Receiver operating characteristic curves of UCP2 for diagnosis of infection/sepsis/septic shock. ROC = receiver operating characteristic, UCP2 = uncoupled protein 2

septic shock by UCP2 is shown in Figure 3. The cut-off value of UCP2 to predict septic shock was 120.66 ng/ml (AUC 0.63, P = 0.095) [95% CI: 0.45, 0.76]. The sensitivity was 53%, the specificity was 66%, the positive predictive value was 0.40, and the negative predictive value was 0.76.

The ROC curve on UCP2 and SOFA for predicting ICU mortality is shown in Figure 4. The study indicated that the AUC of SOFA score was 0.777 [95% CI: 0.65, 0.90] (P = 0.021), and that of UCP2 was 0.664 [95% CI: 0.52, 0.80] (P < 0.001). The mortality in the sepsis group and septic shock group was 15.19% and 29.55%, respectively.

The UCP2 levels correlated with PCT and SOFA score on admission; the correlation coefficient (r) was 0.111 and 0.191 (P 0.337, 0.104) [95% CI: 0.32, 0.116] [95% CI: 0.402, 0.039], respectively; on day 3, r was 0.193 and 0.215 (P = 0.170, 0.127) [95% CI: 0.443, 0.084] [95% CI: 0.461, 0.062], respectively; on day 7, the correlation coefficient between UCP2 and PCT was 0.417 (P = 0.020) [95% CI: 0.672, 0.074]. On day 7, r was negatively correlated between UCP2 and SOFA score, with a value of 0.138 (P = 0.451) [95% CI: 0.221, 0.464).

DISCUSSION

In our study, serum UCP2 concentration had significantly increased in patients with infection, sepsis and septic shock compared to healthy volunteers. The UCP2 level increased with the severity of the disease, indicating its role as a potential early biomarker of sepsis (P < 0.001). However, we could not demonstrate a significant difference in UCP2 levels between the sepsis and septic shock groups.

There is a need for a biomarker to diagnose sepsis early and decrease the associated mortality rate.[7] Huang *et al.*[8] showed that the UCP2 levels were elevated in early sepsis, similar to our study. In the same study, the UCP2 levels showed higher AUC to predict sepsis or septic shock than the SOFA scores and PCT levels on the day of admission. UCP2 is very unstable and has a short half-life of less than 1 h.[9] This emphasises the need for immediate testing of the blood samples for UCP2 levels for better evaluation of this new biomarker. We may also attribute our results to logistic issues, which may have crept in while the samples were collected and stored. A change in the trends

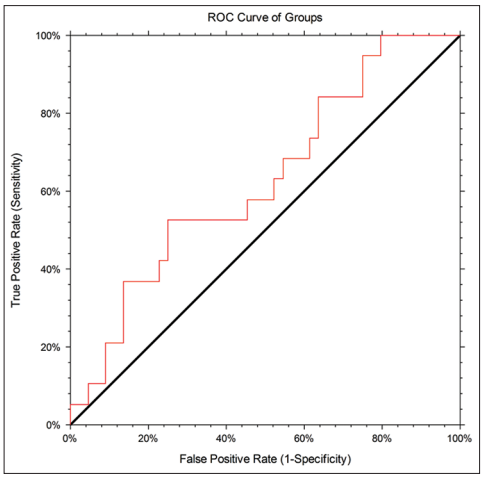

Figure 3: Receiver operating characteristic curve of accuracy of prediction of septic shock by UCP2. ROC = receiver operating characteristic, UCP2 = uncoupling protein 2

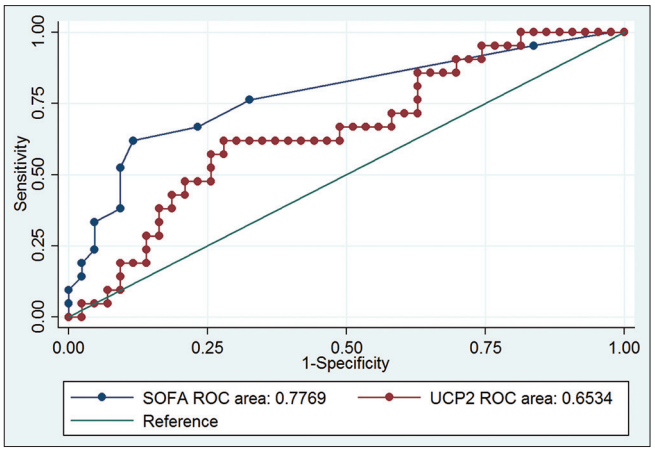

Figure 4: Receiver operating characteristic curve of UCP2 and SOFA scores for predicting ICU mortality. ICU = intensive care unit, ROC = receiver operating characteristic, SOFA = sequential organ failure assessment, UCP2 = uncoupling protein 2

rather than a single reading in very sick patients may give better results. In our study, a blood sample was drawn on the admission day, day 3 and day 7. The patients were partially treated or admitted in critical condition at a tertiary referral hospital. In a study conducted by Jiang *et al.*[6], it was found that UCP2, mRNA and protein were significantly higher in the blood cells of patients with sepsis than in healthy controls. The levels increased with the severity of sepsis and reduced after the treatment.

UCP2 plays an important role in immune cell activation.[10] In sepsis, changes occur in the structural and functional integrity of mitochondria.[4] UCP2 expression increases in conditions that cause mitochondrial dysfunction, such as sepsis.[11] A study by Luo *et al.*[12] on rats, increased UCP2 is a protective factor in early sepsis and helps enhance adenosine triphosphate synthesis. UCP2 also has a protective effect on the mitochondrial damage. Downregulated UCP2 may also suggest a failing heart. The morbidity and mortality in sepsis are related to the cardiovascular system, septic cardiomyopathy being one of the most severe complications.[13-16] We did not correlate echocardiography findings with the UCP2 levels in this study. There was no significant difference in UCP2 levels between sepsis and septic shock patients. One of the possible reasons could be the downregulation of UCP2 levels in patients with septic cardiomyopathy with failing hearts. Various studies have shown that UCP2 expression can be altered in conditions like diabetes, obesity, colon cancer, atherosclerosis, hypertension and smoking. Many drugs like doxorubicin, taxol, metformin and thiazolidinediones also influence the UCP2 levels.[17-20] Hence, increased UCP2 levels need not always indicate early sepsis and must be clinically correlated.

In our study, the UCP2 levels were correlated with PCT and SOFA scores on admission and day 3. This result was similar to those obtained by Huang *et al.*[8] Their study showed a significant correlation between UCP2 and PCT, Acute Physiology and Chronic Health Evaluation (APACHE) II and SOFA score on ICU admission. We observed a significant correlation of UCP2 with PCT only on day 7.

PCT levels have been found to differ between medical and surgical patients with septic shock, with a higher basal level found in surgical patients.[21] Surgical patients with septic shock have a higher threshold level of PCT due to transient bacteremia, endotoxin release or ischaemia. Many of our patients belonged to the SICU. They had undergone debridement for infected wounds or diabetic foot or surgical procedures such as drainage of abscess, laparotomy for peritonitis and stent insertion for pyelonephritis. Hence, PCT in these patients might have been transiently high. The role of PCT in surgical sepsis is questionable.

In the study by Huang *et al.*[8], the AUC of UCP2 to predict 28-day mortality was 0.704, better than the SOFA and APACHE II scores. In our study, the SOFA score better-predicted sepsis than UCP2.

The mean age in the sepsis shock group in our study was significantly higher than that of the sepsis group. Studies have shown that sepsis is predominantly seen in the elderly population with reduced immunity, associated comorbid illness, frailty and malnutrition.[22]

Many of our patients who had undergone surgical procedures belonged to the surgical ICU, which may be the reason for the disparity in the age group. In our study, 82.5% were men. In various studies, the severity and mortality of sepsis concerning gender have shown varied results. Sex hormones may impact innate and adaptive immunity and influence cytokine signalling.[23] Thompson *et al.*[24], in their study, have concluded that men are at an increased risk of sepsis hospitalisation and death when compared to women.

This study has a few limitations. It is an observational study, and the sample size was based on the previous study. An unequal number of patients in the sepsis and septic shock groups could result in statistical errors. Hence, further studies may be required on a larger sample size. Factors such as diabetes, atherosclerosis, smoking, obesity and drugs could affect the level of UCP2. Logistic issues concerning sample collection, testing and pre-hospital treatment could have impacted the UCP2 levels.

CONCLUSIONS

UCP2 levels were significantly elevated in infection, sepsis and septic shock patients in comparison to controls. The UCP2 level increased with the severity of the disease, indicating its role as a potential early sepsis biomarker. There was no significant difference in the UCP2 levels between the sepsis and septic shock groups. UCP2 levels correlated with PCT on admission, day 3 and day 7 of ICU stay.

Study data availability

De-identified data may be requested with reasonable justification from the authors (email to the corresponding author) and shall be shared after approval as per the authors' institution policy.

Acknowledgements

Dr Ramalingappa Antartani, Director KIMS, Hubli, Dr Eshwar Hosmani, Principal KIMS, Hubli, Dr Madhuri S Kurdi, Professor and Head, Department of Anaesthesia, Dr Safiya I Shaikh, Consultant, District Hospital Dharwad, Dr. S.M.Choukimath Associate Professor of pathology, Dr Gurushantappa Yalagachin Professor and Head of Department of Surgery, Dr Bharat, Assistant Professor, Department of Surgery, Dr Asha Patil, Dr Kamkeri, Dr Mahesh DK, Dr Ram Kaulgud, Associate Professor and Nodal Officer, MRU, Dr Alisha M, Dr Aathira AS, Dr Akila, Post graduate students of Anaesthesia, Manjula N, Veeresh Lab Assistants MRU.

Financial support and sponsorship

The study was funded by the Ministry of Science and Technology, Department of Biotechnology, India. The work support was provided by the Multi-disciplinary Research Unit, Karnataka Institute of Medical Sciences, Hubli, Karnataka and Sumukh Prayogalaya, Hubli.

Conflicts of interest

There are no conflicts of interest.

ORCID

Roopa Sachidananda: https://orcid.org/0000-0001-6704-6503

Vikram Kemmannu Bhat: https://orcid.org/0000-0002-7739-391X

Mahantesh Kurjogi: https://orcid.org/0000-0002-1353-1818

Gulam Nabi L Vanti: https://orcid.org/0000-0002-8865-3342

Madhura Kayara: https://orcid.org/0009-0009-6293-3440

REFERENCES

1. Fleischmann-Struzek C, Schwarzkopf D, Reinhart K. Sepsis incidence in Germany and worldwide: Current knowledge and limitations of research using health claims data. Med Klin Intensivmed Notfmed 2022;117:264-8.
2. Shukeri WFWM, Ralib AM, Abdulah NZ, Mat-Nor MB. Sepsis mortality score for the prediction of mortality in septic patients. J Crit Care 2018;43:163-8.
3. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: A systematic review and meta-analysis. Crit Care Med 2006;34:1996-2003.
4. Zhang H, Feng YW, Yao YM. Potential therapy strategy: Targeting mitochondrial dysfunction in sepsis. Mil Med Res 2018;5:41. doi: 10.1186/s40779-018-0187-0
5. Weir EK, Lopez-Barneo J, Buckler KJ, Archer SL. Acute oxygen-sensing mechanisms. N Engl J Med 2005;353:2042-55.
6. Jiang ZM, Yang QH, Zhu CQ. UCP2 in early diagnosis and prognosis of sepsis. Eur Rev Med Pharmacol Sci 2017;21:549-53.
7. Faix JD. Biomarkers of sepsis. Crit Rev Clin Lab Sci 2013;50:23-36.
8. Huang W, Wang X, Zhang H, Wang C, Liu D. The value of serum uncoupling protein-2 level for the patients with sepsis. Shock 2020;54:301-7.
9. Rousset S, Mozo J, Dujardin G, Emre Y, Masscheleyn S, Ricquier D, *et al*. UCP2 is a mitochondrial transporter with an unusual very short half-life. FEBS Lett 2007;581:479-82.
10. Emre Y, Nübel T. Uncoupling protein UCP2: When mitochondrial activity meets immunity. FEBS Lett 2010;584:1437-42.
11. Harrois A, Huet O, Duranteau J. Alterations of mitochondrial function in sepsis and critical illness. Curr Opin Anaesthesiol 2009;22:143-9.
12. Luo S, Li G, Geng Z, Lu Q, Fu B, Fu X. [Effects of uncoupling protein 2 overexpression on myocardial mitochondrial dynamics in sepsis rats]. Zhonghua Wei Zhong Bing Ji Jiu Yi Xue 2019;31:1275-80.
13. Chen ZJ, Song YB, Wang HL, Wang Y, Lv JJ, Che D, *et al*. [Effect of UCP2-siRNA on inflammatory response of cardiomyocytes induced by septic serum]. Zhongguo Dang Dai Er Ke Za Zhi 2014;16:851-5.

14. Hoshovs'ka IuV, Shymans'ka TV, Sahach VF. [Effect of UCP2 activity inhibitor genipin on heart function of aging rats]. Fiziol Zh (1994) 2009;55:28-34.
15. Safari F, Bayat G, Shekarforoush S, Hekmatimoghaddam S, Anvari Z, Moghadam MF, *et al*. Expressional profile of cardiac uncoupling protein-2 following myocardial ischemia reperfusion in losartan- and ramiprilat-treated rats. J Renin Angiotensin Aldosterone Syst 2014;15:209-17.
16. Xu J, Nie HG, Zhang XD, Tian Y, Yu B. Down-regulated energy metabolism genes associated with mitochondria oxidative phosphorylation and fatty acid metabolism in viral cardiomyopathy mouse heart. Mol Biol Rep 2011;38:4007-13.
17. Li J, Jiang R, Cong X, Zhao Y. UCP2 gene polymorphisms in obesity and diabetes, and the role of UCP2 in cancer. FEBS Lett 2019;593:2525-34.
18. Blanc J, Alves-Guerra MC, Esposito B, Rousset S, Gourdy P, Ricquier D, *et al*. Protective role of uncoupling protein 2 in atherosclerosis. Circulation 2003;107:388-90.
19. Busceti CL, Cotugno M, Bianchi F, Forte M, Stanzione R, Marchitti S, *et al*. Brain Overexpression of Uncoupling Protein-2 (UCP2) delays renal damage and stroke occurrence in stroke-prone spontaneously hypertensive rats. Int J Mol Sci 2020;21:4289. doi: 10.3390/ijms21124289.
20. Stanzione R, Forte M, Cotugno M, Bianchi F, Marchitti S, Busceti CL, *et al*. Uncoupling protein 2 as a pathogenic determinant and therapeutic target in cardiovascular and metabolic diseases. Curr Neuropharmacol 2022;20:662-74.
21. Clec'h C, Fosse JP, Karoubi P, Vincent F, Chouahi I, Hamza L, *et al*. Differential diagnostic value of procalcitonin in surgical and medical patients with septic shock. Crit Care Med 2006;34:102-7.
22. Martín S, Pérez A, Aldecoa C. Sepsis and immunosenescence in the elderly patient: A review. Front Med (Lausanne) 2017;4:20. doi: 10.3389/fmed. 2017.00020.
23. Taneja V. Sex hormones determine immune response. Front Immunol 2018;9:1931. doi: 10.3389/fimmu. 2018.01931.
24. Thompson KJ, Finfer SR, Woodward M, Leong RNF, Liu B. Sex differences in sepsis hospitalisations and outcomes in older women and men: A prospective cohort study. J Infect 2022;84:770-6.