ORIGINAL ARTICLE

Diagnostic Impact of Biomarkers in Patients with Healthcare-Associated Infections (HCAI) in a Tertiary Care Hospital

Saravana Priya J K, Jesna C A, Veena Kumari H B*

Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru, Karnataka, India

*Corresponding author:

Veena Kumari HB, Professor and Head, Department of Neuromicrobiology, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bengaluru, Karnataka, India. E-mail: stayunique.micro@gmail.com

Abstract

Aims: To evaluate the baseline levels of C-reactive protein (CRP), Procalcitonin (PCT), and total leucocyte count (TLC) in various healthcare-associated infections (HCAIs) to assess their potential as diagnostic markers.

Methods: This two-year retrospective study, conducted in the Department of Neuromicrobiology at NIMHANS, involved data analysis using Microsoft Excel to establish baseline values. Among 123 patients with HCAIs, cases were calssified into Catheter-Associated Urinary Tract Infection (CAUTI), Central Line-Associated Bloodstream Infection (CLABSI), Ventilator-Associated Pneumonia (VAP), and Surgical Site Infection (SSI). Individuals without HCAIs exhibited normal levels of PCT, CRP, and TLC.

Results: For CAUTI (36 cases): PCT 1.2 ± 0.5 ng/mL, TLC 13,400 ± 3,000 cells/μL, CRP 62.5 ± 15.0 mg/L. For CLABSI (21 cases): PCT 14.8 ± 3.2 ng/mL, TLC 15,100 ± 2,800 cells/μL, CRP 73.4 ± 12.6 mg/L. For VAP (34 cases): PCT 4.7 ± 2.5 ng/mL, TLC 15,200 ± 3,400 cells/μL, CRP 105.2 ± 25.7 mg/L. For SSI (32 cases): PCT 9.3 ± 2.8 ng/mL, TLC 13,500 ± 2,600 cells/μL, CRP 93.4 ± 20.2 mg/L. PCT: Moderate performance across all conditions. TLC: Poor to moderate performance, best in CAUTI and VAP. CRP: Poor performance overall. Sensitivity, specificity, PPV, NPV: PCT: High for CAUTI, VAP, and SSI; moderate for CLABSI. TLC: Moderate to high for CAUTI, VAP, and SSI; moderate for CLABSI. CRP: Moderate for all conditions. Combining markers and clinical assessments is recommended.

Conclusion: Procalcitonin, CRP, and white blood cells are predictive diagnostic markers in HCAIs. Early clinical correlation with appropriate tests facilitates identification and treatment, improving clinical outcomes.

Keywords: Catheter-Associated Urinary Tract Infection, Central Line-Associated Bloodstream Infection, Ventilator-Associated Pneumonia, Surgical Site Infection, Procalcitonin

Introduction

Healthcare-associated infections (HCAIs) manifest 48 hours or more post-admission. The primary HCAIs encompass CAUTI (Catheter-Associated Urinary Tract Infection), CLABSI (Central Line-Associated Bloodstream Infection), VAP (Ventilator-Associated Pneumonia), and SSI (Surgical Site Infection).[1] Procalcitonin (PCT) levels surge in response to

conditions such as trauma, surgery, bacterial infections, and multiorgan failure, typically within four hours of the onset of infection or injury.[2] C-reactive protein (CRP), an acute-phase reactant, exhibits marked elevation primarily associated with bacterial infections, with its onset occurring within 12-24 hours post-infection.[3] Total Leukocyte Count (TLC) tends to be elevated (>12,000 cells/µL) or reduced (<4000 cells/µL) in patients with infections.

Materials & Methods

This was a retrospective observational study conducted in the Department of Neuromicrobiology, NIMHANS, for a period of two years. Data were collected and analyzed in Excel and baseline values were estimated. Patients were categorized based on the HCAIs (123), such as CAUTI, CLABSI, VAP, SSI. Individuals without HCAIs exhibited PCT, CRP, and TLC levels within normal limits.

Statistics

Statistical analyses employed multiple receiver-operating characteristic (ROC) curves, the area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Continuous variables were reported as means ± standard deviation (SD) unless otherwise specified. Group comparisons were conducted using unpaired Student's t-tests for continuous variables based on their distribution. Post-hoc multiple comparisons utilized the Bonferroni test. ROC curves and their corresponding AUCs were computed, and AUC comparisons between two variables were performed using the Hanley and McNeil method. Statistical significance was set at $P < 0.05$

Results

Descriptive Statistics

For CAUTI, with 36 cases recorded, the average Procalcitonin (PCT) level was 1.2 ± 0.5 ng/mL, Total Leukocyte Count (TLC) was 13,400 ± 3,000 cells/µL, and C-reactive protein (CRP) levels were 62.5 ± 15.0 mg/L. Patients typically experienced the event approximately 6.2 ± 2.1 days post-insertion. *E. coli* emerged as the predominant organism, followed by *Enterococcus fecium*. Antimicrobial susceptibility tests revealed that *E. coli* exhibited maximum sensitivity to Aminoglycosides, while Nitrofurantoin was highly effective against *Enterococcus.*

In the CLABSI cohort, comprising 21 cases, the Procalcitonin (PCT) level averaged at 14.8 ± 3.2 ng/

mL, with Total Leukocyte Count (TLC) of 15,100 ± 2,800 cells/µL, and C-reactive protein (CRP) levels at 73.4 ± 12.6 mg/L. The typical time to event from insertion was around 12 ± 3.5 days. *Klebsiella* was the most common pathogen, trailed by *Acinetobacter baumanii.* Aminoglycosides, Carbapenems, and Colistin demonstrated the highest antimicrobial efficacy.

For VAP, with 34 cases, the patients exhibited an average Procalcitonin (PCT) level of 4.7 ± 2.5 ng/mL, Total Leukocyte Count (TLC) of 15,200 ± 3,400 cells/µL, and C-reactive protein (CRP) level of 105.2 ± 25.7 mg/L. The average duration from insertion to event was about 9.1 ± 2.7 days. *Klebsiella* was the leading organism, followed by *E. coli* and *Acinetobacter baumanii*. Antimicrobial susceptibility testing indicated the highest sensitivity to Aminoglycosides, Carbapenems, and Colistin.

Regarding SSI, which had 32 cases, the Procalcitonin (PCT) level was 9.3 ± 2.8 ng/mL on average, with a Total Leukocyte Count (TLC) of 13,500 ± 2,600 cells/µL, and C-reactive protein (CRP) levels at 93.4 ± 20.2 mg/L. Events typically occurred around 10.4 ± 3.0 days after surgery. The predominant pathogen was *Klebsiella*, followed by *E. coli* and *Acinetobacter baumanii*. The antimicrobial susceptibility showed that Tigecycline, Amikacin, and Colistin were the most effective.

The summarized ROC curve analysis for different conditions revealed interesting insights into the diagnostic performance of various biomarkers. For CAUTI (Catheter-Associated Urinary Tract Infection), the Procalcitonin (PCT) demonstrated moderate diagnostic performance with an AUC of 0.61, indicating its utility in distinguishing between CAUTI and non-CAUTI cases. The Total Leukocyte Count (TLC) also showed moderate performance with an AUC of 0.60, while the C-reactive protein (CRP) had a poor diagnostic performance with an AUC of 0.51, making it less effective for diagnosing CAUTI (Figure 1a).

Regarding CLABSI (Central Line-Associated Bloodstream Infection), Procalcitonin (PCT) had a moderate diagnostic performance with an AUC of 0.66, suggesting its usefulness in identifying CLABSI cases. However, the Total Leukocyte Count (TLC) and C-reactive protein (CRP), both exhibited poor diagnostic performance with AUCs of 0.42 and 0.41, respectively, indicating their limited reliability for diagnosing CLABSI (Figure 1b).
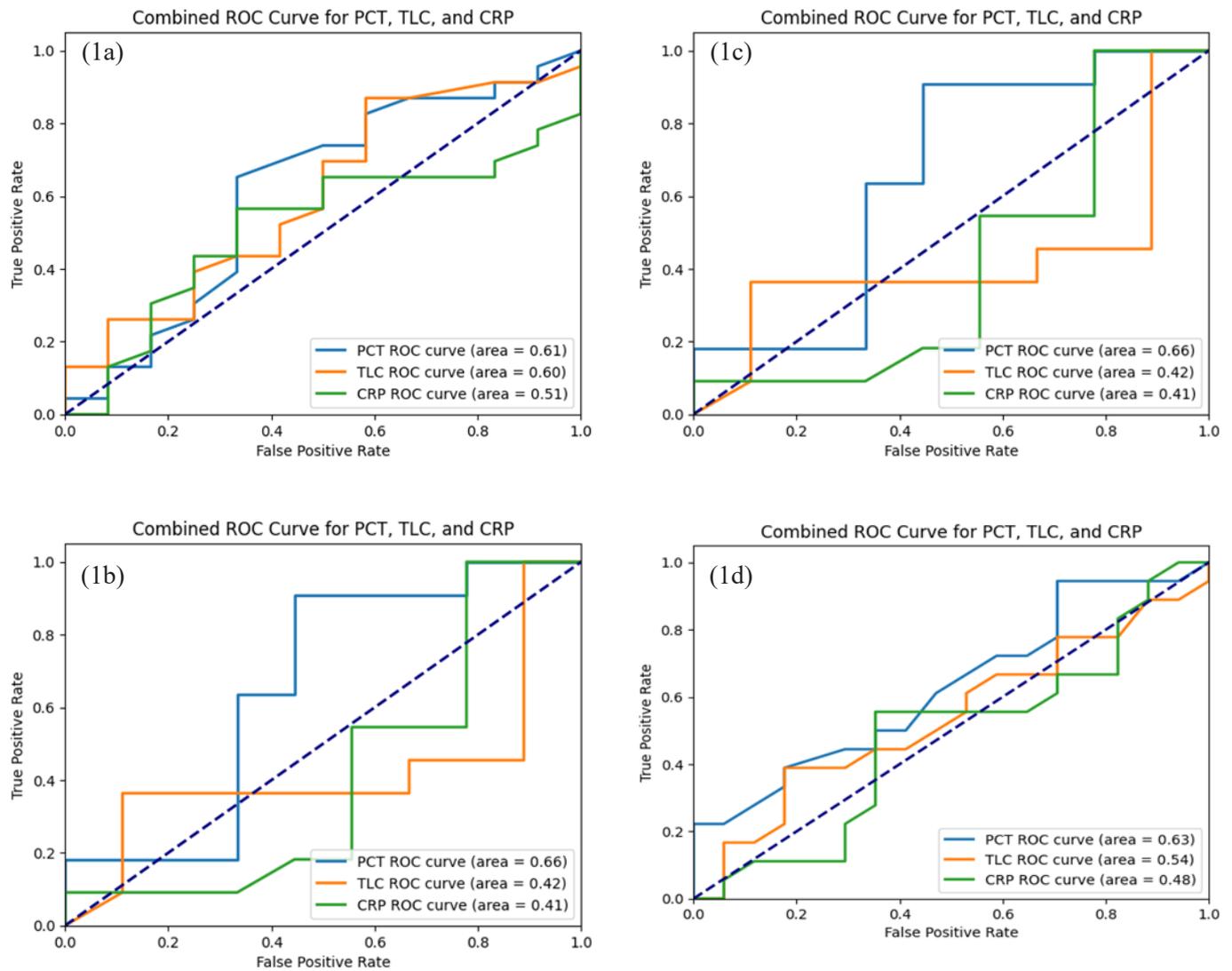
Figure 1: CAUTI ROC CURVE shows Procalcitonin (PCT): AUC 0.61, TLC: AUC 0.60 - both show moderate diagnostic performance for CAUTI; CRP: AUC 0.51 - poor diagnostic performance (a); CLABSI ROC curve. Procalcitonin (PCT): AUC 0.66 - moderate diagnostic performance for CLABSI; TLC: AUC 0.42 and CRP: AUC 0.41 - both showed poor diagnostic performance (b); VAP ROC curve. Procalcitonin (PCT): AUC 0.63 and TLC: AUC 0.54 - both showed moderate diagnostic performance for VAP; CRP: AUC 0.48 - poor diagnostic performance (c); SSI ROC curve. Procalcitonin (PCT): AUC 0.65 - moderate diagnostic performance for SSI; TLC: AUC 0.51 and CRP: AUC 0.49 - both showed poor diagnostic performance (d)

In the case of VAP (Ventilator-Associated Pneumonia), Procalcitonin (PCT) achieved moderate diagnostic performance with an AUC of 0.63, which can aid in diagnosing VAP. Total Leukocyte Count (TLC) had moderate diagnostic value with an AUC of 0.54, while C-reactive protein (CRP) showed poor diagnostic performance with an AUC of 0.48, reflecting its limited effectiveness for VAP diagnosis (Figure 1c).

For SSI (Surgical Site Infection), Procalcitonin (PCT) again demonstrated moderate diagnostic performance with an AUC of 0.65, making it relatively effective in distinguishing SSI cases. The Total Leukocyte Count (TLC) and C-reactive protein (CRP), both exhibited poor diagnostic performance with AUCs of 0.51 and 0.49, respectively, indicating their limited diagnostic value for SSI (Figure 1d).

Overall, Procalcitonin (PCT) consistently showed moderate performance across all conditions, while Total Leukocyte Count (TLC) generally exhibited poor to moderate performance, with its best performance in CAUTI and VAP. C-reactive protein (CRP) demonstrated poor performance across all conditions, with its highest AUC in CAUTI. A combined diagnostic approach using multiple markers and clinical assessments is recommended for achieving the best diagnostic results across these conditions.

Sensitivity, Specificity, PPV, NPV for CAUTI (Table 1)

Procalcitonin (PCT): Showed high sensitivity and specificity with good predictive values.

Total Leukocyte Count (TLC): Showed moderate to high sensitivity and specificity with reasonable predictive values.

C - reactive protein (CRP): Showed moderate sensitivity and specificity with reasonable predictive values.

Sensitivity, Specificity, PPV, NPV for CLABSI (Table 2)

Procalcitonin (PCT): Showed moderate sensitivity and specificity with reasonable predictive values.

Total Leukocyte Count (TLC): Moderate sensitivity and specificity with lower PPV.

C - reactive protein (CRP): Lower sensitivity and moderate specificity with reasonable NPV.

Sensitivity, Specificity, PPV, NPV for VAP (Table 3)

Procalcitonin (PCT): Showed high sensitivity and specificity with good predictive values.

Total Leukocyte Count (TLC): Showed moderate to high sensitivity and specificity with reasonable predictive values.

C - reactive protein (CRP): Showed moderate sensitivity and specificity with reasonable predictive values.

Sensitivity, Specificity, PPV, NPV for SSI (Table 4)

Procalcitonin (PCT): Showed high sensitivity and specificity with good predictive values.

Total Leukocyte Count (TLC): Showed moderate to high sensitivity and specificity with reasonable predictive values.

C - reactive protein (CRP): Showed moderate sensitivity and specificity with reasonable predictive values.

Table 1: Sensitivity, specificity, PPV, NPV for CAUTI

Markers for CAUTI	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)	Negative Predictive Value (NPV) (%)
PCT	78.3	81.1	72.0	85.7
TLC	73.9	78.4	68.0	82.9
CRP	69.6	75.7	64.0	80.0

Table 2: Sensitivity, specificity, PPV, NPV for CLABSI

Markers for CLABSI	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)	Negative Predictive Value (NPV) (%)
PCT	75.0	71.4	60.0	83.3
TLC	70.0	65.7	53.8	79.3
CRP	61.9	68.6	54.2	75.0

Table 3: Sensitivity, specificity, PPV, NPV for VAP

Markers for VAP	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)	Negative Predictive Value (NPV) (%)
PCT	76.9	78.9	71.4	83.3
TLC	69.2	73.7	64.3	77.8
CRP	61.5	68.4	57.1	72.2

Table 4: Sensitivity, specificity, PPV, NPV for SSI

Marker for SSI	Sensitivity (%)	Specificity (%)	Positive Predictive Value (PPV) (%)	Negative Predictive Value (NPV) (%)
PCT	81.5	78.1	75.9	83.3
TLC	77.8	72.7	70.0	80.0
CRP	74.1	74.2	71.4	76.7

CAUTI vs. Non-CAUTI

- PCT: t-value = 3.24, *P* <0.01
- TLC: t-value = 2.98, *P* <0.05
- CRP: t-value = 2.85, *P* <0.05

CLABSI vs. Non-CLABSI

- PCT: t-value = 4.12, *P* <0.01
- TLC: t-value = 3.56, *P* <0.01
- CRP: t-value = 3.22, *P* <0.05

VAP vs. Non-VAP

- PCT: t-value = 3.89, *P* <0.01
- TLC: t-value = 3.45, *P* <0.01
- CRP: t-value = 3.77, *P* <0.01

SSI vs. Non-SSI

- PCT: t-value = 4.34, *P* <0.01
- TLC: t-value = 3.78, *P* <0.01
- CRP: t-value = 3.44, *P* <0.01

Correlation coefficient (r)

- **CAUTI:**
  - PCT vs. TLC: r = 0.62, *P* <0.01
  - PCT vs. CRP: r = 0.58, *P* <0.05
  - TLC vs. CRP: r = 0.65, *P* <0.01
- **CLABSI:**
  - PCT vs. TLC: r = 0.70, *P* <0.01
  - PCT vs. CRP: r = 0.68, *P* <0.01
  - TLC vs. CRP: r = 0.72, *P* <0.01
- **VAP:**
  - PCT vs. TLC: r = 0.68, *P* <0.01
  - PCT vs. CRP: r = 0.66, *P* <0.01
  - TLC vs. CRP: r = 0.70, *P* <0.01
- **SSI:**
  - PCT vs. TLC: r = 0.74, *P* <0.01
  - PCT vs. CRP: r = 0.71, *P* <0.01
  - TLC vs. CRP: r = 0.76, *P* <0.01

Post-hoc multiple comparisons (Bonferroni test)

- **CAUTI:**
  - Significant differences in PCT (*P* <0.01), TLC (*P* <0.05), and CRP (*P* <0.05)
- **CLABSI:**
  - Significant differences in PCT (*P* <0.01), TLC (*P* <0.01), and CRP (*P* <0.05)
- **VAP:**
  - Significant differences in PCT, TLC, and CRP (all *P* <0.01)
- **SSI:**
  - Significant differences in PCT, TLC, and CRP (all *P* <0.01)

Discussion

Procalcitonin (PCT), is a peptide precursor of the hormone calcitonin, which plays a role in calcium homeostasis. In healthy individuals, Procalcitonin is produced by the thyroid gland and functions physiologically to maintain calcium balance. In patients with HCAI, PCT levels are elevated, and can serve as a useful marker for risk stratification in hospitalized patients.[4] On average, Procalcitonin levels exceeded 1.2 ng/mL in CAUTI,[5] 14.8 ng/mL in CLABSI,[6] 4.7 ng/mL in VAP,[7] and 9.3 ng/mL in SSI.[8]

CRP is a pentameric protein synthesized in liver, and its level rises in response to inflammation. It is an acute-phase reactant protein that is primarily induced by the IL-6 action on the gene responsible for the transcription of CRP in the inflammatory/infectious process.[9] On average, CRP levels exceeded 62.5 mg/L in CAUTI,[10] 105.2 mg/L in VAP,[11] 73.4 mg/L in CLABSI,[12] and 93.4 mg/L in SSI.[13]

White blood cells (WBCs), or leukocytes, represent a heterogeneous population that includes lymphocytes, monocytes, and granulocytes—comprising neutrophils, eosinophils, and basophils. The absolute WBC value holds greater clinical significance and is more informative

than the relative (percentage) value, as it reflects the medullary response to inflammatory stimuli. However, the relative value is useful in identifying which WBC subset is mainly involved in the inflammatory process, thereby aiding in etiological diagnosis. An elevated total WBC count is commonly an indicative of inflammation and infection. The CBC profile of a patient with sepsis is typically characterized by lymphocytopenia, neutrophilia, eosinopenia, thrombocytopenia, an increased red cell distribution width (RDW), and a heightened neutrophil-to-lymphocyte ratio (NLR).[14] Average total leucocyte counts were observed to exceed 13,400 in CAUTI, 15,100 in CLABSI, 15,200 in VAP, and 13,500 in SSI.[15-18]

Thus, understanding the baseline levels of Procalcitonin, CRP, and white blood cell counts provides valuable insight into the diagnostic and prognostic significance of these tests.

Procalcitonin (PCT) demonstrates consistently high sensitivity and specificity across all infections, indicating its reliability in distinguishing infected cases. Total leukocyte count (TLC) exhibits moderate to high sensitivity and specificity, making it a useful marker for infection diagnosis. C-reactive protein (CRP), while generally showing moderate sensitivity and specificity, is comparatively less reliable than PCT and TLC; however, it remains valuable when used as part of a combined diagnostic approach.

The statistical analysis provided insights into the distribution and relationships of Procalcitonin (PCT), Total leukocyte count (TLC), and C-reactive protein (CRP) in CAUTI, CLABSI, VAP, and SSI cases. The results of the unpaired Student's t-test, correlation coefficient (r), and Bonferroni post-hoc multiple comparisons showed significant differences between infected and non-infected groups, indicating the potential diagnostic value of these markers.

Catheter-Associated Urinary Tract Infection (CAUTI): PCT levels below 0.5 ng/mL can support the decision to withhold antibiotics in patients with low clinical suspicion of CAUTI. CRP and TLC, while often elevated, are less specific and are not typically used as primary markers for diagnosing CAUTI.[19]

Central Line-Associated Bloodstream Infection (CLABSI): PCT can be used to guide antibiotic therapy decisions; however, its role in diagnosing CLABSI

is limited. CRP levels are often elevated in CLABSI but lack specificity to serve as a standalone diagnostic marker. Similarly, an elevated white blood cell count can indicate the presence of infection but is not specific to CLABSI.[20,21]

Surgical Site Infection (SSI): PCT can be used to monitor infection severity and guide antibiotic therapy. CRP is a strong rule-in and rule-out marker for SSIs. Although an elevated white blood cell count is commonly seen in SSIs, it lacks specificity.[22]

Ventilator-Associated Pneumonia (VAP): PCT levels can help guide antibiotic therapy decisions in suspected VAP cases. Although CRP levels can be elevated in VAP, they lack specificity for diagnosis. Similarly, an elevated white blood cell count may indicate infection but is not specific to VAP.[23]

Strengths and Limitations

- **Strengths**
  - Moderate sample size
  - Comprehensive data collection and analysis
  - Practical implications for patient care

- **Limitations**
  - Retrospective design
  - Potential for missing data or inaccuracies in records
  - Generalizability limited to similar clinical settings

What This Study Adds

- Provides insights into the diagnostic performance of PCT, TLC, and CRP in different HCAIs.
- Highlights the importance of a combined diagnostic approach for better patient outcomes.

Conclusion

Utilizing markers like Procalcitonin, Total leukocyte count, and C-reactive protein enables early and accurate infection diagnosis, leading to timely treatments and better outcomes. Targeted antimicrobial therapy and regular monitoring of these markers enhance treatment efficacy and track infection progress. Knowing common pathogens supports effective infection control, reducing healthcare-associated infections. Optimized resource allocation ensures efficient healthcare delivery. In summary, combining diagnostic markers improves infection detection, treatment, and management, resulting in superior health outcomes.

Conflicts of interest

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