Research article

IG# & IG% in Upper Urinary Tract Infection with Sirs Syndrome Diagnosis, a Retrospective Research at Binh Dan Hospital

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ABSTRACT

Introduction: There have been studies examining the application of immature granulocyte counts (IG#) and immature granulocyte percentage (IG%) indexes, especially in the setting of sepsis originating from various sources. However, to the extent of our knowledge, there are no studies on applying these new indices in sepsis originating from the upper urinary tract. Thus, we conduct this research to evaluate the application IG# & IG% in diagnosing sepsis originating from the upper urinary tract at Binh Dan Hospital.

Purposes: To investigate the role of IG# and IG% in diagnosing sepsis in patients with upper urinary tract infection.

Research Methods: A cross-sectional retrospective research of patients diagnosed with sepsis/septic shock caused by upper urinary tract infection, admitted to Binh Dan Hospital from January 1, 2020, to the end of December 31, 2022. Sepsis 2 (1992) was used to classify those patients into two groups: one with systemic inflammatory response syndrome (SIRS) syndrome and the other with SIRS negative.

Results: 464 cases met the inclusion criteria. 219 patients had SIRS, of which 19 had positive blood cultures and 226 UTIs without SIRS. Results show that IG# and IG% are valuable tools for the initial screening of sepsis originating from upper urinary tract infections. The sensitivity of IG# was 59.7%, and the specificity was 74.3% at the cut-off point of $0.075 \times 10^3/\mu L$. The sensitivity of IG% was 69.3%, and the specificity was 61.9% at the recommended cut-off point of 0.55. When raising the cut-off point of IG% to 1.95, the specificity was 93%. IG#'s AUC is 0.734, IG%'s AUC is 0.692.

Conclusion: Although IG# & IG% cannot be used as a sole biomarker in diagnosing sepsis originating from the upper urinary tract, IG# & IG% are convenient, earliest markers that can help clinicians distinguish between infectious and non-infectious diseases at the time of admission point.

INTRODUCTION

Upper urinary tract infections are not only a common cause of bacteremia or septic shock [1], but are also one of the most common causes of nosocomial sepsis, which can cause death [2]. Severe sepsis, like other diseases with systemic inflammatory response syndrome (SIRS), is characterized by a marked increase in bone marrow neutrophil production (possibly 10-fold) and the appearance of imma-

ture neutrophils in circulation. This is commonly referred to as a "left shift", with an increase in circulating unsegmented (banded) neutrophils of 30%-50% [3]. Lactate, Procalcitonin (PCT) & C Reactive Protein (CRP) are 3 biological tests currently commonly used in combination to diagnose sepsis [4]. However, these additional tests must be ordered and unavailable, causing additional costs and waiting time for the treatment process. The IG tests, including immature granulocyte counts (IG#) and immature granulocyte percentage (IG%), are available on the blood count sheets of the new-generation analyzers. A complete blood count is a routine, basic test covered by Health Insurance (HI) [5]. Therefore, it does not incur additional costs in diagnosis and treatment, and the test results can quickly meet the monitoring needs of clinicians. To our knowledge, no studies have been performed to evaluate new hematological indicators for the early diagnosis of sepsis or septic shock of upper urinary tract origin, so we are performing this research.

METHOD
Research method
Retrospective cross-section.
Research subjects
Vietnamese citizen $\geq$ 16 years old. The sampled population included patients admitted to Binh Dan Hospital from January 1, 2020, to December 31, 2022, and monitored for upper urinary tract infections.
Sampling method
From the list of patients with ICD 10 as septic shock, R.57.2 and N.39, nonspecific site urinary tract infection. Patients with SIRS syndrome had IG#, IG%, and Procalcitonin results were prioritized. The patients were classified into 2 groups: patients with systemic inflammatory response syndrome SIRS according to Sepsis 2 and positive blood culture results. The remaining group was patients without SIRS syndrome & negative blood culture results. Data were processed using SPSS 26.0.

RESULTS
We obtained 464 cases that met the selection criteria, including 219 UTIs with SIRS, 19 cases with positive blood cultures, 226 UTIs without SIRS, and 109 cases that did not meet the selection criteria. of the study (no pyuria or negative urine culture were 43 cases, 1 case was under 16 years old, 8 cases had other major diseases and bacteriuria was comorbidities, 7 cases did not do CBC, 1 was a case of foreigners, 49 cases did not have IG values). Of the 464 eligible records analyzed, 96 had Procalcitonin (PCT) results.

Epidemiologically, these patients came from 36 different provinces of Vietnam, in which Ho Chi Minh City residents accounted for nearly 30% of the patients in the sample. From this sample size, there were 241 male and 223 female patients. The mean age of the patients was 56.67 years (standard deviation 16.07). The youngest patient is 17 years old, and the oldest is 96 years old. In comparing the mean values of the study values between the two groups (Table 1), the

mean value of the group with SIRS syndrome/positive blood culture is often higher than the group with SIRS/negative blood culture, and this statistically significant ($p < 0.05$).

TABLE 1. Anthropometric and laboratory results of the patients.
(* On 96 patients)

	Sample (N = 464)	SIRS/Culture+	SIRS/Culture-
Age	56.67 ± 16.07	55 ± 16.6	58 ± 15.3
Gender Ratio (M/F)	241/223	134/104	107/119
WBC	14 ± 7	17.16 ± 7.2	11.66 ± 5.4
NEU	76 ± 12	81.74 ± 8.9	69.77 ± 12.5
IG#	0.17 ± 0.34	0.25 ± 0.4	0.1 ± 0.14
IG%	1.17 ± 1.87	1.53 ± 2.4	0.8 ± 0.76
PCT*	18.07 ± 31.37	22.5 ± 34.3	7.9 ± 20.4

Blood culture results show that the bacterial spectrum of UTIs is mainly gram-negative (Table 2).

TABLE 2. Blood culture results (of 19 samples).

1	*Klebsiella pneumoniae*	3
2	*Pseudomonas aeruginosa*	2
3	*Stenotrophomonas*	2
4	*Escherichia coli*	4
5	*Escherichia Coli ESBL*	4
6	*Proteus mirabilis*	1
7	*Enterobacter aerogenes*	1
8	*Enterococcus faecalis*	2
	Total	19

In testing the correlation of other health conditions with SIRS/positive blood cultures, our research results are as follows:

TABLE 3. Correlation of health conditions with SIRS/positive blood cultures.

| Health condition	Correlation with SIRS+	p-value
Have JJ	Independence	0.135
Bladder related	Independence	0.137
Kidney stones	Independence	0.14
Urethral stones	Independence	0.44
Urethral stricture	Independence	0.6
Prostate	Independence	0.46
Diabetes	Independence	0.59
Post operation	Independence	0.117
Cancers (undefined)	Independence	0.379
Pregnancy	Dependence	0.014

Pregnancy and having systemic inflammatory response syndrome or septic shock are found to have a correlation relationship statistically significant. The odds ratio between pregnancy and SIRS positive is 3.7.

In the study population, 8 patients were using immunosuppressive drugs or were receiving chemotherapy or radiotherapy when they got sick in this study. In testing the relationship between the use of drugs or immunosuppressive therapy, there was a correlation between patients with systemic inflammatory response syndrome or positive blood cultures with $p = 0.04 < 0.05$. Similarly, in testing the relationship between the use of drugs or immunosuppressive therapy and the treatment outcome, $p = 0.036$. These

parameters demonstrate that suppressing the body's immune system easily increases the risk of infections (specifically, upper urinary tract infections) and, therefore, increases the likelihood of systemic inflammatory response syndrome or sepsis. Immunosuppression might also contribute to treatment outcomes; however, the extent to which this condition affects clinical outcomes is not covered and researched in this study.

TABLE 4. Recommended cut-off point (Youden Index), AUC (Area under the curve), sensitivity, specificity, Diagnosis Odd Ratio, positive predictive value, negative predictive value.
(* Based on 96 cases with procalcitonin values)

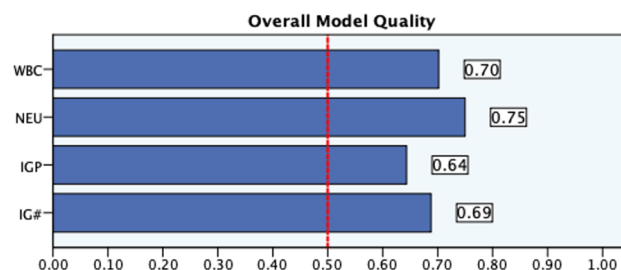|	WBC	NEU	IG#	IG%	PCT*
DOR	9.7	9.014	4.284	3.68	2.59
AUC	0.748± 0.023	0.79± 0.021	0.735± 0.023	0.693± 0.025	0.676± 0.059
Cut off point (Youden index)	12.175	79.65	0.075	0.55	1.26
Sensitivity	85.7%	93.3%	59.7%	69.3%	76.1%
Specificity	61.9%	39.4%	74.3%	61.9%	44.8%
Possitive - Predictive value	70.3%	61.8%	71%	65.7%	76.1%
Negative - Predictive value	80.5%	84.8%	63.6%	65.7%	44.8%
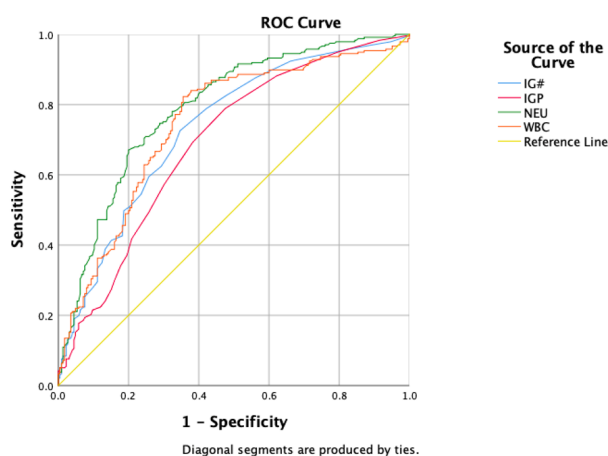
FIGURE 1. Receiver operating characteristic curve.
Compare the diagnostic models of WBC, NEU, IG#, IG% in diagnosing sepsis/septic shock originating from upper urinary tract infection.

DISCUSSION

Leukocytes are important immune response components, helping release important regulatory factors such as cytokines, chemokines, and leukotrienes [6]. Since 1992, WBC has been an important part of the definition of sepsis [7]. However, Sepsis 3 removed WBC and NEU from the diagnostic criteria. Our research results found that the increase in WBC alone or with NEU is still an important part of the pathophysiology of sepsis and the body when there is infection.

Today, the modernity of new-generation blood testing machines helps clinicians know whether or not there is a presence and quantity of immature granulocytes in peripheral blood. Many studies have analyzed the value of the IG# and IG% indices in many different diseases, such as covid 19, sepsis in burn patients, and emergency room patients in many countries. countries in the world such as the US [8], [9], Germany [10], India [6], [11], Brazil [3], Korea [12].

Responding to the call of the authors of previous studies, we are proud to contribute to the literature a study on the above indicators in correlation with sepsis originating from the upper urinary tract. However, after analyzing the data, in general, we see that in diagnosing sepsis caused by the upper urinary tract, the two most valuable biological indicators are white blood cells (WBC) and percent Neutrophil with model values of 0.7 and 0.75, respectively (figure 2), and that IG# & IG% within the limits of this study have higher AUC values than PCT (figure 3).

FIGURE 2. Comparison of diagnostic models for WBC, NEU, IG#, IG%.
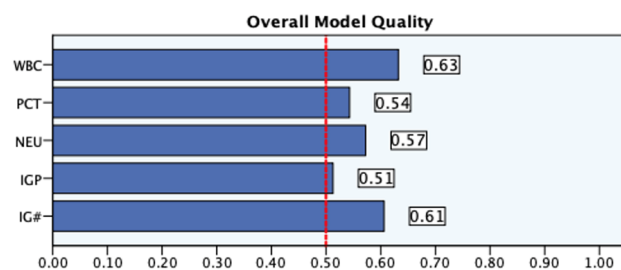
FIGURE 3. Comparison of diagnostic models for WBC, NEU, IG#, IG%, PCT*.
(* over 96 cases with PCT)

From our results, we have the same conclusion as the research of Nierhaus et al. IG# and IG% are valuable in screening, suggesting for clinicians to distinguish between infectious and non-infectious diseases [10]. The mean value of values in the SIRS positive group was higher than in the SIRS negative group, and this difference was statistically significant. However, those prognostic values are not high and, therefore, insufficient to be used as sole, independent biomarkers in the diagnosis of upper urinary tract sepsis.

Due to limited resources, in the sampling method, we were not able to design a study divided into several phases to evaluate changes in indicators through stages of the disease

like in the study of Nierhaus and others [8] nor like that of Bhansaly et al. [5] nor could there be experts to re-evaluate the diagnoses of the patients in the sample. The lack of a gold standard in diagnosis (currently, the use of Sepsis 2 or Sepsis 3 is controversial and is practiced and evaluated differently among clinicians and hospitals around the world) makes it challenging to provide an assessment of the diagnostic accuracy of biomarkers in diagnosing sepsis originating from the urinary tract as well as in comparing the results of current studies. However, research on one center helps limit possible deviations caused by organizational and methodological errors.

The results of the study of Senthilnayagam B and colleagues concluded that compared to WBC, the number of immature granulocytes is a better biological indicator in adults [11]. However, they also emphasized that these results not diagnose sepsis but to predict bacterial sepsis. IG quantity & IG percentage are also effective reference values. Especially IG#, the number of IG# has the same value as WBC (0.69 and 0.7). When running the data of cases with PCT results together, WBC and IG# are the two biological indicators with the best results in the group. Therefore, we conclude that the WBC index has reliable value in screening and diagnosing sepsis originating from the upper urinary tract on a sample size of 464 or when including only 96 individuals.

CONCLUSION

Our study shows the average value of immature granulocyte counts in predicting sepsis in subjects with upper urinary tract infections. However, these indicators can be secondary biomarkers that can be used conveniently and quickly without adding extra work to healthcare workers and saving treatment costs for patients.

CONFLICTS OF INTEREST

None of the authors have conflicts of interest to declare.

REFERENCES

[1] Tran S "Nhiem trung nieu - Bai giang Benh hoc Nieu khoa | Mui Ca Mau publisher, TP.HCM." 1998.

[2] Sabih A, Leslie SW "Complicated Urinary Tract Infections," StatPearls, Nov. 2023, PMID: 28613784. [Online]. Available: https://www.ncbi.nlm.nih.gov/books/NBK436013/

[3] Ayres LS, Sgnaolin V, Munhoz TP "Immature granulocytes index as early marker of sepsis," International journal of laboratory hematology, Jun. 2019, 41:392–396, DOI: 10.1111/IJLH.12990, PMID: 30806482. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/30806482/

[4] Faix JD "Biomarkers of sepsis," Critical reviews in clinical laboratory sciences, Jan. 2013, 50:23–36, DOI: 10.3109/10408363.2013.764490, PMID: 23480440. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/23480440/

[5] eBH "Is blood testing covered by health insurance?" [Online]. Available: https://ebh.vn/bao-hiem-y-te/xet-nghiem-mau-co-duoc-huong-bao-hiem-y-te

[6] Bhansaly P, Mehta S, Sharma N et al. "Evaluation of Immature Granulocyte Count as the Earliest Biomarker for Sepsis," Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine, Feb. 2022, 26:216–223, DOI: 10.5005/JP-JOURNALS-10071-23920, PMID: 35712744. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/35712744/

[7] Bone RC, Balk RA, Cerra FB et al. "Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine," Chest, 1992, 101:1644–1655, DOI: 10.1378/CHEST.101.6.1644, PMID: 1303622. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/1303622/

[8] Karon BS, Tolan NV, Wockenfus AM et al. "Evaluation of lactate, white blood cell count, neutrophil count, procalcitonin and immature granulocyte count as biomarkers for sepsis in emergency department patients," Clinical biochemistry, Nov. 2017, 50:956–958, DOI: 10.1016/J.CLINBIOCHEM.2017.05.014, PMID: 28552399. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/28552399/

[9] Crouser ED, Parrillo JE, Seymour C et al. "Improved Early Detection of Sepsis in the ED With a Novel Monocyte Distribution Width Biomarker," Chest, Sep. 2017, 152:518–526, DOI: 10.1016/J.CHEST.2017.05.039, PMID: 28625579. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/28625579/

[10] Nierhaus A, Klatte S, Linssen J et al. "Revisiting the white blood cell count: immature granulocytes count as a diagnostic marker to discriminate between SIRS and sepsis–a prospective, observational study," BMC immunology, 2013, 14, DOI: 10.1186/1471-2172-14-8, PMID: 23398965. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/23398965/

[11] Senthilnayagam B, Kumar T, Sukumaran J et al. "Automated measurement of immature granulocytes: performance characteristics and utility in routine clinical practice," Pathology research international, 2012, 2012, DOI: 10.1155/2012/483670, PMID: 22448336. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/22448336/

[12] Jeon K, Lee N, Jeong S et al. "Immature granulocyte percentage for prediction of sepsis in severe burn patients: a machine leaning-based approach," BMC infectious diseases, 2021, 21, DOI: 10.1186/S12879-021-06971-2, PMID: 34915849. [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/34915849/