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Research paper

Usefulness of granulocyte parameters for diagnosis of sepsis among patients with Systemic Inflammatory Response Syndrome

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Key words: granulocyte parameters, Systemic inflammatory response syndrome, diagnosis, sepsis

Abstract

Sepsis is a major cause of mortality and is the primary cause of death from infection in critically ill patients. Accurate diagnosis and early treatment of sepsis is very important to prevent rapid progression to multi organ failure, septic shock and death. Patients with infections can progress to Systemic Inflammatory Response Syndrome (SIRS). Early identification and close monitoring of patients with SIRS is important as this may be the initial presentation of sepsis. In clinical practice it is difficult to differentiate between non-infectious systemic inflammation and sepsis, because many clinical signs overlap in both conditions. There is no "gold standard" test to detect sepsis throughout the world.

Therefore, this study was carried out to determine the usefulness of granulocyte parameters for the diagnosis of sepsis among adult patients with SIRS. This was a descriptive cross-sectional study which included 234 adult patients admitted to medical wards of Teaching Hospital Karapitiya, Sri Lanka with features of SIRS. Patients with sepsis were identified according to the Third International Consensus criteria for sepsis. Absolute neutrophil count (ANC), toxic changes and immature granulocyte percentage (IG%) were assessed in each study subject. Statistical analysis was performed using SPSS software. Study subjects were grouped into two on the basis of presence and absence of sepsis. Neutrophil parameters of two groups were compared to assess the significance. Comparisons of means were done using independent two sample T test for continuous variables and Chi-Square test for categorical variables.

There was no statistically significant association between ANC and sepsis (p=0.858 [p>0.05]). A statistically significant association was found between presence of toxic changes and sepsis (p=0.00 [p<0.05]). In the study population, the mean IG% was1.57% and standard deviation was 2.75. There was a statistically significant association between IG% and sepsis (p=0.001 [p<0.05]). Neutrophil toxic changes and IG% can be used to differentiate sepsis in SIRS patients with a greater certainty. However, further studies are needed to confirm the usefulness of these parameters in a diverse setup.

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to an infection[1]. It is a complex, life threatening condition that arises when the body's response to an infection damages its own tissues and organs. Sepsis can be differentiated from infection by the presence of organ failure and dysregulated or abnormal host response. Organ failure can be assessed using Sequential (sepsis related) Organ Failure Assessment Score (SOFA score)[1]. Acute change in total SOFA score 2 or more due to an infection is used to identify organ dysfunction. Clinical criteria used for confirmation of sepsis is presence of 2 or more SOFA points (above baseline) in a patient with proven infection[1].

In critically ill patients, sepsis is a major cause of mortality and morbidity and it is the primary cause

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death from infection[2]. Estimated global dence of sepsis is 3 per 1000 population per year h an estimated annual mortality between 50 deaths per 100,000 population. In general, pital population with presumed infection, overall mortality risk of sepsis is approximately 10%[2,3]. Sepsis can progress to septic shock and death. Patients with septic shock have a mortality over 40%[1]. Therefore, accurate diagnosis and early treatment of sepsis is very important to prevent rapid progression to multi organ failure, septic shock and death.

Patients with sepsis can initially present with the Systemic Inflammatory Response Syndrome (SIRS). It is defined as a clinical response to a nonspecific insult of either infectious or non-infectious origin[4]. Early identification and close monitoring of patients with SIRS are important as this may be the initial presentation of sepsis. In practice, it is difficult to differentiate between non-infectious systemic inflammation and sepsis, because evidence of microbiological infection is often ambiguous and many clinical signs overlap in both conditions.

Various studies have been carried out throughout the world to look for factors that help to diagnose sepsis, yet there is no "gold standard" test to detect sepsis. Therefore, various serological markers such as C-Reactive Proteins (CRP), procalcitonin (PCT), IL6 and IL8 have been studied to help rapid identification of patients with sepsis. But use of these are not practical due to cost, limited availability and time consumption[5,6].

In an appropriate clinical context, positive blood culture is considered diagnostic of sepsis. Relatively long incubation period is the major disadvantage of blood cultures. Also, false negative results can be caused by insufficient quantity of blood, inappropriate culturing conditions for fastidious organisms and presence of antibiotics or other inhibitory factors in the blood samples. False positive results are also due to errors in collection or processing of samples[7].

Therefore, it is important to have other laboratory parameters to predict sepsis and bacteraemia. A full blood count is invariably performed on admission as well as used for the monitoring of patients with suspected sepsis/SIRS throughout the hospital stay. If granulocyte parameters can be used to diagnose sepsis, it will be useful for the clinicians to implement optimum management

A study done by Porizka et al evaluated the usefulness of immature granulocyte percentage (IG%) to discriminate between postoperative non-infective systemic inflammatory response syndrome (SIRS) and sepsis. The results showed the best cut-off value for IG% of 1.45% (sensitivity 70.5%, specificity 60%) and 1.43µg/l for PCT (sensitivity 65.9%, specificity 75%). The combination of IG% and PCT provided the best sepsis prediction (area under the curve of 0.8, sensitivity 63.6% and specificity 88.8%)[8].

A study on immature granulocytes index as an early marker of sepsis, reported IG% of 2% with statically significant association with sepsis (p=0.00 [p<0.05])[9]. In a study which evaluated the role of neutrophil and monocyte volume, conductivity and scatter (VCS), derived from automated haematology analysers, in critically ill patients with suspected sepsis showed VCS parameters may help to strengthen the diagnostic probability of sepsis[10].

In a case control study, which assessed the Neutrophil-lymphocyte ratio in the early diagnosis of sepsis in an intensive care unit revealed association of sepsis with the presence of a neutrophil lymphocyte ratio greater than 5.0, leukocyte count above $12x10^9$/L and band neutrophil percentage above 10%[11].

A study on immature granulocytes index as early marker of sepsis reported statically significant association with sepsis and IG% of 2% (p=0.0 [p< 0.05])[9].

However, such studies were sparse in Sri Lanka and use of novel automated FBC parameters in clinical decision making are not freely used. Therefore this study was carried out to assess the usefulness of the absolute neutrophil count, immature granulocyte percentage and toxic changes in neutrophils in predicting sepsis among patients with SIRS. There are no published studies on this topic in Sri Lanka to date.

Materials and methods

This was a descriptive study among patients admitted to medical wards, at the Teaching Hospital, Karapitiya. Adult patients (patients above 12 years were considered as an adult) admitted to medical wards, Teaching Hospital, Karapitiya with features of Systemic Inflammatory Response Syndrome (SIRS) were included into this study until minimal sample size was achieved.

Patients with two or more of the following features were considered as having SIRS. Temperature >38°C or <36°C, heart rate >90/min, respiratory rate >20/min or $PaCO_2$ <32 mm Hg and white blood cell count <$4x10^9$/L or >$12x10^9$/L or immature bands >10%. Patients with white blood count of 4x10 – $12x10^9$/μL were included into the study if they fulfilled other criteria for SIRS.

Adult patients with SIRS without an obvious cause for SIRS who consented for the study were recruited. Patients with obvious causes for SIRS (e.g.: trauma, myocardial infarction etc) were excluded.

Minimum number of patients needed to be studied was calculated using $n=Z^2 \sigma^2 / d^2$ formula. (According to a pilot study mean absolute neutrophil count in septic patients was $17.4x10^9$/L and standard deviation was $7.8x10^9$/L). Minimal sample size was 234.

Adult patients admitted to medical wards at the Teaching Hospital, Karapitiya with features of Systemic Inflammatory Response Syndrome during the period of January to September 2017 were included into the study until minimum sample size of 234 was reached.

Data collection was done by the principal author. Basic characteristics of patients, relevant examination findings and the investigations carried out during the hospital stay including series of FBC performed, were recorded on patients with SIRS.

Therefore, on admission and day-3 FBC and blood picture were used to assess absolute neutrophil count and immature granulocyte percentage. In the haematology laboratory, blood picture slides which were prepared for verification of the analyser findings were used to assess neutrophil toxic changes by the principal author. Neutrophil toxic changes assessed included, toxic granules, vacuoles and Dohle bodies. Accumulation of large, dark granules in segmented neutrophils or sometimes in earlier neutrophil precursors are called toxic granules. Neutrophil toxic changes were randomly verified by another senior registrar in clinical haematology.

Dohle bodies are sky-blue cytoplasmic inclusions in neutrophils[12].

Immature granulocyte percentage and absolute neutrophil count were assessed from data available in Mindray BC-6800 automated blood cell counter.

Morphological assessment of immature granulocyte percentage was done. Band forms were not included into the immature granulocyte fraction.

Among SIRS patients, patients who had evidence of infection (focus of infection-culture positive urinary tract infection [UTI] or symptoms of UTI with positive urine full report, blood stream infections [positive blood culture], pneumonia, infective endocarditis, meningitis, skin and soft tissue infections or bone or joint infections) and SOFA score of 2 or more above the base line were considered as having sepsis. Patients without above 2 criteria were considered as having SIRS without sepsis (according to the third international consensus definitions for sepsis and septic shock).

Ethical approval for the study was obtained from the Ethical Review Committee, Faculty of Medicine, University of Ruhuna, Sri Lanka. There was no additional blood collection from patients for the research. Informed consent was obtained from patients or relatives of the critically ill patients. Anonymity of the patients and confidentiality of data were maintained.

Statistical analysis and results

FBC and blood picture findings of 234 patients of SIRS were analysed using SPSS (Statistical package) 20 version. Granulocyte parameters on SIRS

patients, with and without sepsis were analysed separately. Comparisons of means were done using independent two sample T test for continuous variables and Chi-Square test for categorical variables.

Patients with sepsis were identified according to the Third International Consensus Criteria for Sepsis[1].

A total number of 234 patients were included into the study. There were 134 (57.3%) male and 100 (42.7%) female patients. Age range of study subjects was from 15 to 94 years, patients' median age was 58.3 years. There were 66 (28.2%) patients below 50 years and 168 (71.8%) patients above 50 years. Majority of patients (62, 26.4%) were above 70 years.

Among 234 patients with SIRS, 118(50.4%) patients had sepsis. The number of patients without sepsis was 116 (49.6%).

The commonest focus of infection was urinary tract infection (UTI) (22.2%), followed by pneumonia (16.2%), pyelonephritis (9.4%), cellulitis (7.3%) and lower respiratory tract infections (6.4%). Focus of infection could not be identified in 34 (14.5%) patients with SIRS.

Blood smears were evaluated to assess neutrop toxic changes. Toxic changes were identified in 14 (59.8%) patients. There were 94 (40.2%) Sep patients without toxic changes. Among 140 Sep patients with toxic changes, 72.2% had only toxi granules and 27.9% had both toxic granules an vacuoles. Dohle bodies were not identified i blood smears examined.

In the study population, WBC count was range from 3.3x10^9 /l to 43.5x10^9 /l. The mean WBC cou was 15.9x10^9/l (standard deviation was 6.9). Amon 118 patients with sepsis, the majority (80, 67.8% had WBC count above 12.0x10^9/l and only 3(2.5% had WBC equal or below 3.9x10^9/l.

The absolute neutrophil count in the study popu lation ranged from 1.90x10^9/l to 37.2x10^9/l. Mean neutrophil count was 12.9x10^9/l and standar deviation was 6.5. The majority (196, 83.8%) ha neutrophil count above 7.5x10^9/l.

In the study population, immature granulocyte percentage ranged from 0.00% to 27.80%. The mean immature granulocyte percentage was 1.57% and standard deviation was 2.75.

Comparisons of means were done using inde pendent two sample T test for continuous varia bles and Chi-Square test for categorical variables

Table1. Absolute neutrophil count and presence and absence of sepsis in study subjects

Absolute neutrophil count	With sepsis	Without sepsis	Total
=/<2.5 x10^9/l	3 (2.5%)	0 (0%)	3 (1.3%)
2.6-7.5 x10^9/l	23 (19.5%)	12 (10.3%)	35 (15.0%)
>7.5 x10^9/l	92 (78.0%)	104 (89.7%)	196 (83.8%)
Total	118 (100%)	116 (100%)	234 (100%)

Chi-Square test was used to assess the association between toxic changes and sepsis.

Table 2. Toxic changes in the study population

Toxic changes	Sepsis	
	Present No. (%)	Absent No. (%)
Present	85 (72.0%)	55 (47.4%)
Absent	33 (28.0%)	61 (52.6%)
Total	118 (100%)	116 (100%)

X^2 =14.75, df=1, p=0.00(p<0.05)

Higher number of patients with sepsis had toxic changes. There was a statistically significant association (p=0.00 [p<0.05]) between presence of toxic changes and sepsis.

Independent two samples T test was used to assess the association between mean WBC count and sepsis (Table 3), mean absolute neutrophil count and sepsis (Table 4) and immature granulocyte percentage and sepsis (Table 5).

Table 3. Mean WBC count and presence/ absence of sepsis in study subjects

Sepsis	Number of patients	Mean WBC	Standard deviation
Present	118	15.954	8.0027
Absent	116	15.924	5.8015

t=0.033, df=232, p=0.974 (P> 0.05)

Patients with sepsis and without sepsis had mean WBC count of 15.954x10^9/l and 15.924x10^9/l respectively. There was no statistically significant association (p=0.974 [p>0.05]) between the mean WBC count and presence of sepsis.

Table 4. Association between mean absolute neutrophil count and presence and absence of sepsis in the study population

Sepsis	Number of patients	Mean ANC	Standard deviation
Present	118	12.9833	7.2332
Absent	116	12.8311	5.69501

ANC-Absolute Neutrophil Count t=0.179, df =232, p=0.858 (p>0.05)

There was no statistically significant difference between absolute neutrophil count of patients with without sepsis. Patients with sepsis had mean absolute neutrophil count of 12.98x10⁹/l while pat without sepsis had mean absolute neutrophil count of 12.83x10⁹/l.

Patients with sepsis had mean immature granulocyte percentage (IG%) of 2.1713, whereas mean IG non-sepsis group was 0.9644. There was a statistically significant association (p=0.001 [p<0.05]) betw IG% and presence of sepsis.

Table 5. Association between IG% and presence / absence of sepsis in study subjects

Sepsis	Number of patients	Mean IG %	Standard deviation
Present	118	2.1713	3.54851
Absent	116	0.9644	1.34516

IG%-Immature Granulocytes percentage t=3.451, df=232, p=0.001(p<0.05)

Discussion

Full Blood Count (FBC) is routinely evaluated in patients with suspected SIRS at less cost than other laboratory markers of sepsis. This study evaluated the usefulness of granulocyte parameters for diagnosis of sepsis among patients with SIRS.

In the study population, majority of patients were males (57.3%) while females were 42.7%. Male: female ratio was 1.3:1. According to a study done by Cornbleet et al showed male: female ratio of 1.63:1[13] which was higher compared to this study. Among 234 patients, 62 (26.4%) were above 70 years. Only 39 (16.6%) were below 40 years. In the study population, patients' median age was 58.3 years. A study done by Grozdanovski et al reported median age of 58.1 years[14] which was almost similar to this study population.

The commonest focus of infection was UTI (22.2%). There were 34 patients (14.5%) with unknown focus. According to a study done by Grozdanovski et al in a tertiary care university hospital in Macedonia, the commonest source of infection was lower respiratory tract (57.8%) and there were 5.1% of patients with unknown focus[14]. Indian study done in ITU settings showed higher incidence of respiratory tract infections (37.2%) and focus of infection was unknown in 12%[15].

According to this study and the Indian st revealed unknown focus in 14.5% and 12% patients respectively. These two figures were cl to each other but different to the results Macedonian study which showed only 5.1% patients with unknown focus of infection.

In the study sample, 118 patients had sepsis, wh was 50.4% of the sample. A Korean study done Yoonmi et al showed different proportions patients with SIRS and sepsis which were 26.7 and 73.29% respectively[2].

In this study population, 83.7% of patients h absolute neutrophil count above 7.5x10⁹ Absolute neutrophil count was above 7.5x10⁹/l 78% and 89.7% of patients with and without sep respectively. The mean absolute neutrophil cou was 12.9x10⁹/l. A study done by Martins et showed mean absolute neutrophil count of 10.8 10⁹/l [11].

According to our data there is no statistical significant association between absolute neut phil count and sepsis (p=0.85 [p > 0.05]). However this finding was different to the results of the st done by Martins et al which showed statis significant association between absolute neut phil count and sepsis (p=0.018 [<0.05])[11], whi need further evaluation.

The toxic changes were identified in 140 (59.8%) patients with SIRS. There was a statistically significant association between presence of toxic changes and sepsis (p=0.00 [p<0.05]). There were no similar studies to compare the results of toxic changes and sepsis after an extensive search on international and local literature.

In the study population, mean immature granulocyte percentage was 1.57% with standard deviation of 2.75. There was a statically significant association between immature granulocyte percentage and sepsis (p=0.001 [p< 0.05]). These results were consistent with studies carried out in different regions of the world. A study done in Czech Republic showed immature granulocyte percentage of 1.45% (p=0.01)[8]. A German study showed immature granulocyte percentage of 1.58% (p=0.0001)[16], while a Brazil study reported immature granulocyte percentage of 2% (p=0.001)[17].

Conclusion

Granulocyte parameters are useful for diagnosis of sepsis among patients with Systemic Inflammatory Response Syndrome.

There is no statistically significant association found between sepsis and absolute neutrophil count, while statistically significant association is evident between toxic changes and immature granulocyte percentage with presence of sepsis (p<0.05). Neutrophil toxic changes and immature granulocyte percentage can be used to detect patient with sepsis.

However, further studies are useful to assess association of sepsis with toxic changes and immature granulocyte percentage, before using them as indicators of sepsis in clinical settings.

Limitations and recommendations

There could be patients with sepsis who remain undetected due to false negative blood cultures. Procalcitonin is a widely used bio marker to detect patients with sepsis, but it was not available during the study period.

External quality assurance was not available in the government sector for immature granulocyte percentage during the period of data collection.

External quality assurance is recommended for immature granulocyte percentage for validation of data.

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Authorship

Contribution: TMKCS wrote the proposal, carried out the data collection, performed data analysis and wrote the manuscript. Authors MM and KACW corrected the proposal, supervised and guided the methodology and corrected the manuscript.

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References

1. Mervyn S, Inger, Clifford SD, Christopher WS, Manu SH, Djillali H, Michael B, Rinaldo B, Gordon RB, Jean DC, Craig M, Coopersmith, Richard S, Hotchkiss, Mitchel IM, Levy, John C, Marshall, Greg S, Martin, Steven M, Opal, Gordon D, Rubenfeld, Tom P, Jean LV, Derek C, Angus. The Third International Consensus Definitions for Sepsis and Septic Shock. *JAMA* 2016; **315**(8): 801-10.
2. Yoonmi S, Jong RC, Juwon K, Young KK, Jongwook L, Jaewoo Song, Sue JK, Kyung AL. Delta neutrophil index: A promising diagnostic and prognostic marker for sepsis. *Shock* 2012; **37**(3): 242-46.
3. Andrew L, Iain M. Sepsis: definition, epidemiology, and diagnosis. *BMJ.* 2007; **335**(1): 879-83.
4. Lewis JK. Systemic inflammatory response syndrome. (last updated August 2016) Cited: available

from:emedicine.medscape.com/article/168943-overview.

5. Jeong AR, Jeong HY, Daesang L, Chi MP, Gee YS, Kyeongman J, Joongbum C, Sun YB, Keumhee CC, Chi RC. Clinical usefulness of procalcitonin and C-Reactive Protein as outcome predictors in critically ill patients with severe sepsis and septic shock. *PLOS ONE*. 2015; **10**(9): 1-12.

6. Konrad R, Michael B, Niels C, Riedemann, Christiane SH. New approaches to sepsis: Molecular diagnostics and biomarkers. *CMR* 2012; **25**(4): 609-34.

7. Ali AL, Thomas SK, Michael JB. Immature granulocyte measurement using the Sysmex XE-2100. Relationship to infection and sepsis. *Am J Clin Pathol.* 2003; **120**(1): 795-99.

8. Porizka M, Volny L, Kopecky P, Kunstyr J, Waldauf P, Balik M. Immature granulocytes as a sepsis predictor in patients undergoing cardiac surgery. *Interactive Cardio Vascular and Thoracic Surgery* 2019; **28**(6) 1-7.

9. Ayres LS, Sgnaolin V, Terezinha P. Immature granulocytes index as early marker of sepsis. *International Journal of Laboratory Haematology.* 2019; **41**(8) 21-8.

10. Mammen J, Choudhuri J, Paul J, Sudarsan TI, Josephine T, Mahasampath G, Jeyaseelan V, Nair SC, Peter JV. Cytomorphometric neutrophil and monocyte markers may strengthen the diagnosis of sepsis. *Intensive Care Med.* 2018; **33**(12): 656-62.

11. Martins EC, Silveira LF, Viegas K, Beck AD, Junior GF, Cremonese RV, Lora PS. Neutrophil-lymphocyte ratio in the early diagnosis of sepsis in an intensive care unit: a case-control study. *Revista Brazileira De Terapia Intensiva*. 2019; **31**(1): 63-70.

12. Szakmany T, Pugh R, Kopczynska M, Lundin RM, Sharif B, Morgan P, Ellis G, Abreu J, Kulikouskaya S, Bashir K, Galloway L, Al-Hassan H, Grother T, McNulty P, Seal ST, Cains A, Vreugdenhil M, Abdimalik M, Dennehey N, Evans G, Whitaker J, Beasant E, Hall C, Lazarou M, Vanderpump CV, Harding K, Duffy L, Guerrier Sadler A, Keeling R, Banks C, Ng SWY, Heng SY, Thomas D, Puw EW, Otahal I, Battle C, Minik O, Lyons RA, Hall JE. Defining sepsis on the wards: results of a multi-centre point prevalence study comparing two sepsis definitions. *Anaesthesia.* 2018; **73**(2): 195-204.

13. Cornbleet PJ. Clinical utility of the band count. *Clin Lab Med.* 2002; **22**(1): 101-32.

14. Grozdanovski K, Milenkovic Z, Demiri I, Sp... Prediction of outcome from Community-ac... severe sepsis and septic shock in tertiary... university hospital in a developing Country. C... *Care Research and Practice*. 2012; **20**(6): 6-7.

15. Paary TTS, Kalaiselvan MS, Renuka MK, Arun... AS. Clinical profile and outcome of patients... severe sepsis treated in an Intensive Care U... India. *Ceylon Medical Journal* 2016; **61**(4): 181...

16. Nierhaus A, Klatte S, Linssen J, Eismann... Wichmann D, Hedke J, Braune SA, Kluge S. Rev... the white blood cell count: immature granulo... count as a diagnostic marker to discriminate bet... SIRS and sepsis. *BMC Immunol.* 2013; **12**(4) 14...

17. Kristine K. Toxic changes. *Pathology student* ... **12**(2) 8-10.

18. Seventh World Health assembly update, 2017... Available from https://www.who.int/news-ro... detail/30-05-2017-seventieth-world-hea... assembly-update-30-May-2017

19. Mitaka C. Clinical laboratory differentiatio... infectious versus non-infectious Systemic Infl... matory Response Syndrome. *Clin Chim Acta.* 2... **351**(1-2): 17-29.

20. Kelly GN, Mary AOR, Eleanor JM, Michele CW, Li... MS. Performance of an Automated immat... granulocyte count as a predictor of neonatal se... *Am J Clin Pathol.* 2005; **123**(4): 618-24.

21. Aikaterini D, Zaina K, Hulyan T, Dyanne D, Dmitr... Jean LV, Olivier P. Volume, Conductivity and Sca... Properties of Leukocytes (VCS Technology) in Dete... Sepsis inCritically Ill Adult Patients. *Blood* 2... **118**(21): 47.

22. Nathan K, Edward AW. Immature neutrophils in... blood smears of young febrile children. *J... Pediatrics* 1999; **153**(3): 261-66.

23. Soon ML, Ho SE, Ran N, Min SP, Kook IP, Ch... Usefulness of the delta neutrophil index for asse... neonatal sepsis. *Acta Paediatrica* 2013; **12**... 13-6.

24. Sivagnanasundram C. Learning Research. 1st... Sivagnanasundram; 1999.

25. Lewis JM, Abouyannis M, Katha G, Nyirenda... Chatsika G. Population incidence and mortalit... sepsis in an urban African setting 2013-2016. *Cli... Infect Disease* 2019; **21**(9) 12-7.