ABSTRACT
Bacterial infections in the elderly are deadly if late detected. Several age-related immunological changes make this population more prone to infection and have atypical presentation when infected. Biomarkers are commonly used to aid in diagnosing bacterial infection in the elderly, given their subtle clinical presentation. However, traditional biomarkers such as leukocyte, Erythrocyte Sedimentation Rate (ESR), and C-Reactive Protein (CRP) lack specificity and some biomarkers level are influenced by medication use. Procalcitonin, a preprocalcitonin derivative, is elevated in the presence of bacterial infection and not affected by the immunosuppressive drug. Procalcitonin is a promising marker for detecting bacterial infection in the elderly. This review tries to describe the rationale and value of procalcitonin to diagnose and prognosticate bacterial infection in the elderly.

KEYWORDS
Procalcitonin, Elderly, Bacterial Infection, Diagnostic, Prognostic

Introduction
Demographic data changes show an increase in the number of elderly population number worldwide. In Western countries, the elderly population accounts for nearly a quarter of emergency room visit.[1,2] Bacterial infection, mainly pneumonia, is still the highest cause of mortality and morbidity in the elderly.[3] However, deterioration of immune status in the elderly (immunosenescence) causes a non-specific symptom in an infected elderly patient such as fall, functional status impairment, shortness of breath, incontinence, syncope, anorexia, or delirium.[1,2] Delayed antibiotics administration due to initial misdiagnosis will lead to even higher mortality.

Some of the commonly used parameters for bacterial infections are not helpful in the elderly population. White Blood Cell count is an unreliable parameter as the count can be normal or change slightly at the early of infection. In elderly patients with cholecystitis, 41% of patients do not have leukocytosis.[4] C-reactive protein (CRP) can be used for early detection of infection because its level begins to rise six hours after bacterial infection with a peak after 48 hours. However, CRP levels can also be elevated after physical trauma and active inflammatory disease. Other conditions associated with increased CRP level are pulmonary embolism, deep vein thrombosis, acute myocardial infection, malignancy, rheumatoid arthritis, and autoimmune diseases. CRP level can also decrease in the patient using corticosteroid or non-steroidal anti-inflammatory drug (NSAIDs).[5]

Procalcitonin, a peptide with 116 amino acids, is a precursor of calcitonin. Calcitonin is a hormone synthesized by C cells (parafollicular) from the thyroid gland and used in calcium metabolism. In active infection, procalcitonin is released by parenchymal cells in response to bacterial toxins. Procalcitonin shows an increased level in early infection and show a more rapid decline when the infection has been controlled. Procalcitonin is associated with the degree and extent of infection and has a prognostic factor in critically ill patients. Another advantage of procalcitonin is its level is not significantly affected by the administration of corticosteroid or NSAID, and it is not affected by immunosenescence which frequently occurs among the elderly.
elderly.[6] However, most studies about the diagnostic value of procalcitonin were conducted in the children and young adults population. Few studies trying to find the diagnostic value of procalcitonin in elderly patients have yielded controversial result.[7,8]

**Immunosenesence and infection in elderly**

Changes in demographic data around the world are causing an increase in the elderly population. The improvement of Indonesia’s health care system has led to an increase in life expectancy from 67.1 in 2000 to 70.8 in 2010 and is expected to reach 73.3 in 2025.[1,9] Consequently, there will be an increasing number of elderly populations who need medical assistance when sick. In Western countries, a quarter of emergency room visit was contributed by the elderly.[2] The elderly have a higher risk of infection than young adult. Several things thought to play a role are immunological changes, functional status changes, body reserve capacity reduction, and multipathology. Fundamental changes in the immune system related to aging are known as immunosenesence. Immunosenesence causes a decrease of immune status and dysregulation of its response to infection at multiple levels.[1,10] Changes in the immune system related to aging are listed in Table 1.[11,12]

Elderly patients who had bacterial infection experience a blunting in local and systemic responses and present with different clinical characteristics. Patients may present with decreased functional or mental status, anorexia, acute exacerbation of existing chronic diseases (congestive heart failure, chronic pulmonary obstructive disease, diabetes mellitus), falls, shortness of breath, incontinence, or syncope.[2,10] Fever is not found in 30% of the elderly population with a bacterial infection. This is probably due to a blunting of temperature changes response along with increasing age. A decrease in basal body temperature coupled with a reduction in inflammatory response will make the elderly rarely present with increased body temperature. The existence of cognitive dysfunction in the elderly will aggravate the existing problem because the patient can’t express their symptom.[10]

Early recognition and prompt treatment of bacterial infection in the elderly are crucial. Currently, available evidence shows a better outcome in patient who get prompt and appropriate antimicrobial treatment. In septic patients, antibiotics should be given within the first hour, especially after blood cultures are taken and adjusted within the next 48-72 hours. Furthermore, not all elderly patients who appear septic have an infection. Antibiotics administration in this population can cause new problems in antibiotic resistance, drug toxicity, and high medical costs.[7,13] Therefore, there is an urgent need for an effective and accurate marker of bacterial infection in the elderly.

**Infection marker in elderly**

Biomarkers are used to detect bacterial infection in the elderly, given the subtle clinical feature of infection in this population. Leukocytosis, which is often used as an infection parameter, may be absent or slightly increased. This is probably related to reduced leucocyte mobilization capacity during acute stress in geriatric patients. In addition, there is also a decrease in neutrophil enzymes number released during degranulation. One study of elderly patients with cholecystitis found no leukocytosis in 41% of the subjects. Leukocytosis is not a specific parameter for bacterial infection. It can be caused by inflammation, tissue necrosis, myeloproliferative disease, malignancy, thyroid disorder, and several drugs such as epinephrine and corticosteroids.[1,4,14]

Erythrocyte Sedimentation Rate (ESR) is a non-specific parameter for bacterial infection. However, further evaluation is needed in patients with very high ESR. Apart from acute infection, chronic infection, chronic inflammatory disease, collagen vascular disease, and malignancy can also cause an increase in ESR. In patients with bacterial infection, serial ESR examination is an inexpensive and simple way to monitor therapeutic response. An important highlight is that in patients whose ESR level does not decrease after antibiotics therapy, even though the clinical condition has improved, it may result from the patient’s comorbidities/chronic condition.[15]

C-reactive protein (CRP) is an acute-phase reactant that is produced by the liver as a result of the reaction to Interleukin-6 (IL-6) and other pro-inflammatory cytokines. CRP titer begins to rise 6 hours after bacterial infection and peaks after 48 hours. The uniqueness of CRP is its half-life which is not influenced by patient’s comorbidities so that it can be used for therapy monitoring in the elderly. However, there is another condition that can lead to an increased CRP such as physical trauma, active inflammatory condition, pulmonary embolism, deep vein thrombosis, acute myocardial infection, malignancy, rheumatoid arthritis, and autoimmune diseases. CRP has higher sensitivity to predict early bacterial infection in the elderly compare to leukocyte count. One study found CRP level ≥ 60 is a good cut-off for detecting bacterial infection in the elderly.[1,5]

**Procalcitonin as an infection marker in the elderly**

In healthy individuals, procalcitonin is produced by thyroid C cells and coded by the CALC-1 gene located on chromosome 11. Preprocalcitonin, its precursor, will be converted into 116 amino acids procalcitonin, which later will be cut into three molecules: active calcitonin, catacalcin, and N-terminal procalcitonin. The calcitonin hormone will be used in calcium and phosphorus metabolism. Normally, all procalcitonin will be converted into calcitonin and released into circulation. Therefore, under normal circumstances, the blood procalcitonin level is very low (0.05 ng/mL). Several regulatory mechanisms affect procalcitonin releases, such as increased calcium, steroid use, glucagon, or beta-adrenergic receptor stimulation. During inflammation, procalcitonin release is not affected by its nor-
Table 1 Immune system changes related with aging[11,12]

| Immune system changes related with aging[11,12] | Age-related decline | Age-related increase |
|-------------------------------------------------|----------------------|----------------------|
| Innate Immunity                                 | Neutrophils oxidative burst | Neutrophils bacterial phagocytosis |
|                                                | Macrophages chemotaxis |  |
|                                                | Macrophages phagocytosis |  |
|                                                | NK cell cytotoxicity |  |
|                                                | NK cell cytokine production |  |
|                                                | Macrophages cytokine production |  |
|                                                | NK cell number |  |
|                                                | Macrophages phagocytosis |  |
|                                                | Macrophages cytokine production |  |
| Plasmacytoid dendritic cells cytokine release   |  |  |
| PBMC delayed response                           |  |  |

| Adaptive Immunity                               | Peripheral naive T cell and B cell number | Memory T cell and memory B cell number |
|                                                | T cell repertoire diversity | Adiposity in thymus |
|                                                | B cell variety | Ig G and Ig A serum level |
|                                                | IL-7 production | CD8 cell |
|                                                | Ig M and Ig D serum level | IL-6, IL-1β, TNF-α serum concentration |
|                                                | CD4 cell | Autoreactive serum antibodies |

Procalcitonin as bacterial infection marker in elderly: recent evidence

To date, several studies are investigating the use of procalcitonin as a bacterial infection marker in the elderly. A 2013 meta-analysis by Lee et al.,[8] of 4 prospective studies involving 760 geriatric patients with suspected bacterial sepsis found sensitivity and specificity of 0.83 (95% CI: 0.38-0.98) and 0.83 (95% CI: 0.60-0.94), respectively. This meta-analysis obtained an AUROC of 0.89 (95% CI: 0.86-0.92), which is a good score for diagnostic tests. Among four studies included, three studies used 75-year-old benchmark, and one study used 65-year-old benchmark. The quality of these four studies was calculated using the QUADAS instrument gave good results with a score of more than 10. The positive predictive value for the procalcitonin test was 4.77 (95% CI: 2.49-9.13), with a negative predictive value of 0.20 (95% CI: 0.04-0.97). There was significant heterogeneity with I2of 68.0% (95% CI: 67.95–6.86). This may be due to the use of different procalcitonin cut-off between the four studies. Subgroup analysis by limiting studies with the same cut-off value, study setting, and age yielded an interesting result. Two studies in the emergency unit set had a high sensitivity of 0.97 but low specificity of 0.61. In comparison, the other two studies in the ward setting had low sensitivity of 0.46 but high specificity of 0.94. The advantage of this study is that it includes the positive likelihood ratio and negative likelihood ratio values. The procalcitonin’s positive likelihood ratio of 4.77 is not high enough to diagnose a bacterial infection. Still, a negative likelihood ratio of 0.20 is low enough to rule out a bacterial infection, especially in populations with a low probability of sepsis. This study also found that the accuracy of procalcitonin for elderly patients with sepsis is non-inferior to that in adult patients.

Gomez-Cerquera et al. [19] conducted a study to assess the validity of procalcitonin to diagnose bacterial infection in the elderly. The study involved 161 patients over 65 years of age divided into groups with possible bacterial infection and group and CRP, procalcitonin levels are not affected by corticosteroid or non-steroidal anti-inflammatory drugs. However, some non-infectious conditions can increase procalcitonin levels, such as ischemic heart disease, heart failure, kidney failure, and malignancy.[6,16,19]

Figure 2: Procalcitonin production in inflammatory state.
without infection. In the infection group, 76% of patients met the criteria for sepsis, and 48% of patients met the criteria for severe sepsis. This study found that 72% of patients with bacterial infection had PCT levels >0.5 ng/ml, and 41% of patients had PCT levels >2ng/ml, while in the non-infection group, only 8% of patients had PCT levels >0.5ng/ml. The main highlight is all patients without bacterial infection had a glomerular filtration rate below 60ml/ment/1.73 m2. Procalcitonin cut-off value of 0.5 ng/ml is considered the most representative of bloodstream bacterial infection with sensitivity of 72% (95%CI: 62-81%), specificity of 92% (95%CI: 85-100%), PPV of 93% (95%CI: 82-97%), and NPV of 70% (95%CI: 56-80%). A positive likelihood ratio of 9 with a negative likelihood ratio of 3 indicates that procalcitonin is a good indicator for diagnosing bacterial infection in an emergency unit setting, especially to rule out a bacterial infection in patients with atypical symptoms.

The latest study by Shokouhi et al. [20] tried to find diagnostic and prognostic value of procalcitonin in adult patients with bacteremia. This study divided 406 subjects into two categories, patients with bacteremia and without bacteremia. Furthermore, this study classifies the case and control group into the population aged below 65 years and over 65 years. All patients were followed for up to 28 days, and mortality was calculated. This study obtained a procalcitonin cut-off of 0.09 for adult patients and 0.08 for elderly patients (Sensitivity and specificity 82.6% and 82% respectively in adult and 69.1% and 70% respectively in the elderly). The procalcitonin's Area Under the Curve (AUC) as a predictor of 28-day mortality was 0.82 (95% CI: 0.70-0.94; p<0.001), which reflects that procalcitonin can be used as a predictor of short-term mortality in elderly patients with a bacterial infection. The cut-off value of 0.2 in both adult and the elderly can be used (Sensitivity and specificity 81% and 81.7% respectively in adult and 75% and 80.4% respectively in the elderly).

Conclusion

The manifestations of bacterial infection in elderly patients are often atypical, necessitating the use of biomarkers. Procalcitonin can be used in elderly patients with non-inferior diagnostic value compared to the general adult population. Procalcitonin can also be used to rule out sepsis in low prevalence populations of sepsis. However, given its imperfect diagnostic value, the interpretation of procalcitonin in a high-risk population of sepsis should be carried out with caution and adjusted to the clinical context.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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