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# D-Dimer Levels and Prognostic Features in Pulmonary Embolism

Burak Kurtoğlu[1], Halil Ibrahim Cıkrıklar[2], Vahide Aslıhan Durak[2], Issa Malongo Omar[3], Ahmet Munir Yılmaz[2], Sümeyye Tuğba Sarkı Cander[4], Erol Armagan[2]
[1] Bursa City Hospital, Bursa, Turkey.
[2] Bursa Uludag University Medical Faculty, Emergency Medicine Department, Bursa,Turkey.
[3] Bursa Yıldırım Doruk Hospital, Bursa,Turkey.
[4] Dr. Ersin Arslan Training And Research Hospital, Gaziantep, Turkey.

## Abstract

**Background:** The aim of our study is to investigate the efficacy of D-dimer marker in patients who applied to the emergency department with a preliminary diagnosis of pulmonary embolism.

**Materials and methods:** This study was conducted retrospectively at Bursa Uludağ University Faculty of Medicine Hospital between January 2018 and December 2018. Patients whose D-dimer levels were checked considering the preliminary diagnosis of pulmonary embolism were included in the study.

**Results:** A total of 3411 patients were included in the study. In all patients, the diagnosis of PE was made by computed tomography pulmonary angiography. Examination of 1968 patients with (+) D-dimer revealed new diagnosis in 702 patients (35.67%). Pulmonary embolism was diagnosed in a total of 74 patients (10.54%) whereas the most common alternative diagnoses was 33.62% (n=236) pneumonia. On examination of 1443 patients with negative D-dimer levels, pulmonary embolism was diagnosed in 7 (3.14%) patients whereas the most common other diagnoses was 44.84% (n=100) Acute Coronary Syndrome. However, in the D-dimer positive patient group, the rate of newly diagnosed patients requiring clinical and intensive care hospitalization was found to be significantly higher.

**Conclusion:** In conclusion, even if pulmonary embolism is not detected in D-dimer positive cases, it is thought that these patients need further investigation, considering the frequency of serious conditions requiring clinical and intensive care unit admission.

**Keywords:** Emergency medicine, pulmonary embolism, D-Dimer

## Introduction

D-dimer is a fibrin degradation end product and plasma D-dimer levels increases as a result of thrombosis and fibrin breakdown. Balance exists between fibrin formation and degradation under physiological conditions. Hence, plasma D-dimer level may be a biological indicator of hemostatic abnormalities and thrombosis[1].

D-dimer levels may be elevated in thrombotic diseases such as Pulmonary Embolism (PE) and Venous Thromboembolism (VTE). D-dimer is one of the diagnostic parameters in PE and Deep Vein Thrombosis (DVT)[2]. A high D-dimer level alone is not sufficient to diagnose PE. However, it can be used to exclude PE in patients with a low or moderate probability of PE[3]. The specificity of D-dimer in confirming the diagnosis of PE and DVT is low[2].

Comorbidities such as cancer, inflammatory diseases, infection, aortic dissection, pneumonia, and renal failure are pathological causes that affect D-dimer levels. Pregnancy and age are non-pathological causes affecting D-dimer levels[4].

A D-dimer concentration of ≥500 ng/mL is considered positive and <500 ng/mL is considered negative[5]. D-dimer levels increase with age. Therefore, the specificity of the D-dimer test is reduced in elderly patients (> 50 years). Many studies recommends the formula; Age x 10 = ng/mL, for threshold value in patients over 50 years of age[6]. For patients considered to be at low risk of PE, a normal D-dimer (<500 ng/mL) effectively excludes PE and typically no further testing is required[3].

The aim of our study is to determine the relationship between the prognostic features and existing comorbidities of patients who admit to the emergency department with preliminary diagnosis of PE, and thus to investigate the effectiveness of D-dimer marker.

## Materials and Methods:

This study, which was conducted retrospectively with the approval of Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee, dated 16 June 2021,

**Corresponding Author:** Halil İbrahim Çıkrıklar **e-mail:** halilcikriklar@gmail.com
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number 2021-8/25 (Annex-1), within the scope of specialization thesis. A total of 3411 patients over the age of 18 years, who appiled to Uludag University Faculty of Medicine Emergency Service between January 2018 and December 2018 with a pre-diagnosis of PE and D-dimer levels examined, were included.

The list of patients whose D-dimer levels were investigated within the specified date was obtained from the electronic medical record system. Patient information was obtained from Uludağ University electronic medical record system and calculated according to age, gender, plasma D-dimer concentration and pregnancy status. The D-dimer cut-off value, was determined according to patients' new diagnosis, ongoing diseases and hospitalization-discharge information.

500 ng/ml plasma D-dimer concentration was accepted in young patients whereas the corrected formula (Age x 10 = ng/mL) was used in elderly (≥ 50 years) patients.

These values and above were considered D-dimer positive, while those below these values were considered D-dimer negative. D-dimer threshold value in pregnant women was accepted as 1000 ng/ml. In all patients, the diagnosis of PE was made by computed tomography pulmonary angiography.

Patients under the age of 18, patients whose D-dimer examination was requested with diagnoses other than PE, patients whose D-dimer value could not be determined due to coagulation of the sample or low amount, and repeated admissions of the same patient were not included in the study.

In calculating the sample size of the study, Power was determined by taking at least 80% and Type-1 error 5% for each variable. Descriptive statistics for the categorical variables in the study were expressed as mean, standard deviation, numbers (n) and percentages (%). Chi-square test was calculated to determine the relationships between D-Dimer level and other categorical variables. Statistical significance level (a) was taken as 5% in the calculations and SPSS (IBM SPSS for Windows, ver.25) statistical package program was used for analysis.

## Results

A total of 3411 patients; 1963 male (57.5%) and 1448 female (42.5%), were included in the study. The mean age was calculated as 59.74 (+/-18.08).

Examination of 1968 patients with (+) D-dimer revealed new diagnosis in 702 patients (35.67%), whose distribution is shown in Table-1.

As seen in the table, PE was diagnosed in a total of 74 patients (10.54%) and the most common other diagnoses were 33.61% (n=236) pneumonia and 13.96% (n=98) ACS, respectively. Other less common diseases are arterial embolism, intracranial hemorrhage, gastrointestinal bleeding, urinary tract infection, bone fracture, aortic dissection and sepsis. Out of 925 newly diagnosed patients in the emergency department, 315 (34.05%) were admitted to the Intensive Care Unit (ICU), 410 (44.32%) hospitalized, while 188 (20.32%) patients were discharged.

**Table 1:** Distribution of new diagnoses in D-dimer positive patients.

| | | (+) D-Dimer | | *p. |
|---|---|---|---|---|
| | | N | % | |
| Primary New Diagnosis | PN | 236 | 33,61% | ,001 |
| | ACS | 98 | 13,96% | |
| | PE | 74 | 10,54% | |
| | DVT | 32 | 4,55% | |
| | ARI | 31 | 4,41% | |
| | PLE | 27 | 3,84% | |
| | CVD | 22 | 3,13% | |
| | CEL | 21 | 2,99% | |
| | ML | 18 | 2,56% | |
| | PX | 8 | 1,13% | |
| | ELT | 5 | 0,71% | |
| | AP | 3 | 0,42% | |
| | OTHER | 127 | 18,09% | |
| | TOTAL | 702 | 100% | |

** Significance level according to Pearson Chi-square test results*
PN: Pneumonia
ACS: Acute Coronary Syndrome
PE: Pulmonary Embolism
ARI: Acute Renal Insufficiency
DVT: Deep Vein Thrombosis
PLE: Pleural Effusion
CVD: Cerebrovascular Disease
CEL:Celult
ML: Malignant
PX: Pneumothorax
ELT: Electrolyte Disorder
AP: Acute Appendicitis

In 1522 (77.34%) of the D-dimer positive patients, additional problems developed on the basis of existing diseases were detected and treated. The distribution of these diseases is shown in Table-2.

As seen in the table, the most common accompanying diseases were malignancy in 24.57% (n=374), Coronary Artery Disease (CAD) in 14.38% (n=219) and hypertension in 12.68% (n=193) respectively. Other less common diseases are previous history of CVD, previous history of PE, cirrhosis, heart valve replacement and Alzheimer's.

No emergency pathology was detected in 1146 (58.23%) patients with positive D-dimer and they were discharged with recommendations after their initial evaluation.

Examination of 1443 patients with negative D-dimer revealed new diagnoses in 223 patients (15.45%) and their distribution is shown in Table 3.

As seen in the table, PE was diagnosed in 7 (3.13%) patients, while the frequency of most common other diagnoses was 44.84% (n=100) ACS and 24.21% (n=54) pneumonia, respectively. Other less common diseases were arterial em-

**Table 2:** Comorbidities in D-dimer positive patients

| | | (+) D-Dimer | | *p. |
|---|---|---|---|---|
| | | N | % | |
| Eski tanı | ML | 374 | 24,57% | ,001 |
| | CAD | 219 | 14,38% | |
| | HT | 193 | 12,68% | |
| | COPD | 139 | 9,13% | |
| | DM | 115 | 7,55% | |
| | HF | 98 | 6,43% | |
| | CRF | 97 | 6,37% | |
| | RM | 51 | 3,35% | |
| | AST | 26 | 1,70% | |
| | DVT | 15 | 0,98% | |
| | EPL | 5 | 0,32% | |
| | OTHER | 190 | 12,48% | |
| | TOTAL | 1522 | 100% | |

** Significance level according to Pearson Chi-square test results*
ML: Malignant
CAD: Coronary Artery Disease
HT: Hypertension
COPD: Chronic Obstructive Pulmonary Disease
DM: Diabetes Mellitus
HF: Heart Failure
CRF: Chronic Renal Failure
RM: Rheumatological Disease
AST: Asthma
DVT: Deep Vein Thrombosis
EPL: Epilepsy

**Table 3:** Distribution of new diagnoses in patients with negative D-dimer.

| | | D-Dimer (-) | | *p. |
|---|---|---|---|---|
| | | N | % | |
| Primary New Diagnosis | ACS | 100 | 44,84% | ,001 |
| | PN | 54 | 24,21% | |
| | PX | 8 | 3,58% | |
| | PE | 7 | 3,13% | |
| | CEL | 7 | 3,13% | |
| | AP | 5 | 2,24% | |
| | ML | 4 | 1,79% | |
| | CVD | 3 | 1,34% | |
| | ELT | 3 | 1,34% | |
| | ARI | 2 | 0,89% | |
| | DVT | 2 | 0,89% | |
| | OTHER | 25 | 11,21% | |
| | TOTAL | 223 | 100% | |

** Significance level according to Pearson Chi-square test results.*
ACS: Acute Coronary Syndrome
PN: pneumonia
PX: Pneumothorax
PE: Pulmonary Embolism
CEL: Cellulite
AP: Acute Appendicitis
ML: Malignant
CVD: Cerebrovascular Disease
ELT: Electrolyte Disorder
ARI: Acute Renal Failure
DVT: Deep Vein Thrombosis

bolism, pleural effusion, atrial fibrillation, gastrointestinal bleeding, intracranial hemorrhage. Out of 223 newly diagnosed patients in the emergency department, 95 (42.6%) were admitted to the ICU, 70 (31.4%) to relevant clinics, while 54 (24.2%) patients were discharged.

In 806 (55.85%) of negative D-dimer patients, additional problems developing on the basis of existing diseases were detected and treated. Their distribution is shown in Table-4.

As seen in the table, the most common accompanying diseases were CAD in 19.35% (n=156), hypertension in 16.50% (n=133), malignancy in 12.90% (n=104) and COPD in 12.28% (n=99). Other less common diseases are previous history of PE, atrial fibrillation, previous history of CVD and valve replacement. When 806 cases with previously diagnosed diseases were evaluated; 92 patients (11.4%) were treated in ICU whereas 81 patients (10.0%) were hospitalized in relevant clinics. While 5 (0.6%) patients refused treatment and left the emergency department, a total of 628 (77.9%) patients were discharged. No pathology was detected 1207 (83.64%) patients with negative D-dimer and they were discharged with recommendations after their initial evaluation.

A comparison of the results of D-dimer positive and D-dimer negative patients is shown in Table 5 and Figure 1.

As seen in the Table 5 and Figure 1, 17.17% (n=338) of D-dimer positive patients were admitted to the ICU, while 23.53% (n=463) were hospitalized. 8.80% (n=127) of patients with negative D-dimer were admitted to the intensive

**Table 4:** Comorbidities in D-dimer negative patients.

| | | D-Dimer (-) | | *p. |
|---|---|---|---|---|
| | | N | % | |
| Eski Tanı | CAD | 156 | 19,35% | ,001 |
| | HT | 133 | 16,50% | |
| | ML | 104 | 12,90% | |
| | COPD | 99 | 12,28% | |
| | DM | 76 | 9,42% | |
| | RD | 34 | 4,21% | |
| | HF | 33 | 4,09% | |
| | CRF | 24 | 2,97% | |
| | AST | 22 | 2,72% | |
| | DVT | 15 | 1,86% | |
| | EPL | 11 | 1,36% | |
| | OTHER | 99 | 12,28% | |
| | TOTAL | 806 | 100% | |

** Significance level according to Pearson Chi-square test results.*
CAD: Coronary Artery Disease
HT: Hypertension
ML: Malignant
COPD: Chronic Obstructive Pulmonary Disease
DM: Diabetes Mellitus
RD: Rheumatological Disease
HF: Heart Failure
CRF: Chronic Renal Failure
AST: Asthma
DVT: Deep Vein Thrombosis
EPL: Epilepsy

**Table 5:** Comparison of the results of D-dimer positive and D-dimer negative patients

| | | (-) D-Dimer | | (+) D-Dimer | | *p. |
|---|---|---|---|---|---|---|
| | | N | % | N | % | |
| Result | DS | 1207 | 83,65% | 1146 | 58,23% | ,001 |
| | ICU | 127 | 8,80% | 338 | 17,17% | |
| | CLN | 101 | 7,00% | 463 | 23,53% | |
| | TR | 8 | 0,55% | 14 | 0,71% | |
| | EX | 0 | 0,00% | 5 | 0,25% | |
| | UA | 0 | 0,00% | 2 | 0,10% | |
| | TOTAL | 1443 | 100% | 1968 | 100% | |

** Significance level according to Pearson Chi-square test results.*
DS: Discharge
ICU: Intensive care unit
CLN: Clinic
TR: Treatment rejection
EX: Exitus
UA: Unauthorized abandonment

care unit, while 7.00% (n=101) were hospitalized. D-dimer was positive in 13 out of 28 pregnats patients without any additional pathology.

In this study, the sensitivity of D-dimer was 91.36%, specificity 43.12%, positive predictive value 3.76%, and negative predictive value 99.51%, respectively.

## Discussion

The D-dimer test is best used in conjunction with clinical probability assessment in the diagnosis of PE. The negative predictive value of the D-dimer test, studied with quantitative methods, is high and a normal D-dimer level excludes acute PTE or DVT with a sensitivity of >95%, especially in outpatients, patients without comorbidities, and with low and moderate clinical probability[7,8].

The specificity of plasma D-dimer level is low[9]. In our study, PE was diagnosed in only 74 of 1968 D-dimer positive cases. However, for patients considered to be at low risk of PE, a normal D-dimer (<500 ng/mL) effectively excludes PE and usually no further testing is required in this regard[8]. In our study, PE was diagnosed in 7 out of 1443 negative D-dimer cases. In this study, the sensitivity of D-dimer was 91.36%, specificity 43.12%, positive predictive value 3.76%, and negative predictive value 99.51%.

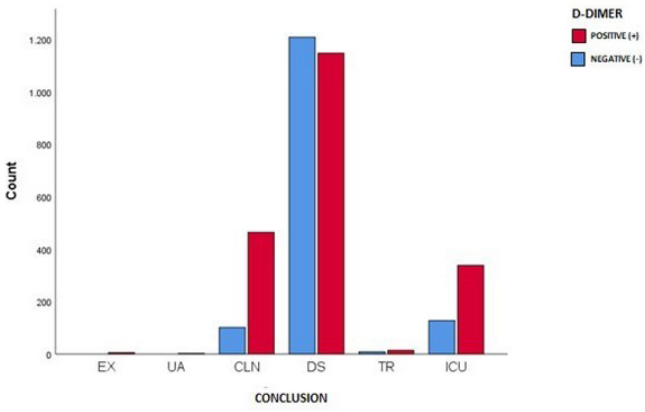


**Figure 1:** D-dimer positive patients

D-dimer levels increases in advanced ages (>50 years)[9]. In a multinational prospective study, the proportion of patients in whom PTE could be excluded without false-negative findings was reduced from 6.4% to 30% by adding 10 mg/L to age, instead of the standard 500 mg/L D-dimer level in patients aged> 50 years[10]. In our study, we used the age-adjusted formula when determining the threshold value for old patients.

Acute diseases increases D-dimer levels[9]. In a study by Giuseppe Lippi et al. including 1647 patients who admitted to the emergency department and D-dimer levels checked with a preliminary diagnosis of VTE, the most common diagnoses were 15.6% infection, 12.1% VTE, 9.4% syncope, 8.9% cardiac failure, 8.2% trauma and 5.8% malignancy respectively[11]. In the study of Halide Akbaş et al. involving 671 patients, the most common diagnoses in patients with high D-dimer levels who admitted to the emergency department were 19% infection, 15.9% heart and circulatory diseases, 12.9% non-specific diseases, 12% atypical chest pain, 10.7% malignancy and 7.6% PE respectively[12]. Likewise, in our study, PE was diagnosed only in 74 patients (10.54%), while the most common diagnoses were 33.61% (n=236) pneumonia and 13.96% (n=3). 98) ACS.

Cancer is an important cause of venous thrombosis[13]. Levitan et al., in their study, reported a high incidence of VTE in cancer patients[14]. Elderly patients with lung cancer complicated with PE have dyspnea, chest pain, and/or hemoptysis[15]. These findings are similar to the clinical presentation of PE[16]. As a matter of fact, in our study, malignancy was detected in 18 patients (2.56%) in the newly diagnosed positive D-dimer group, while the most common accompanying disease was malignancy with a rate of 24.57% (n=374) out of 1522 patients with a previous diagnosis.

Studies have concluded that there is a positive correlation between plasma D-dimer levels and stroke[17]. Joan Montaner et al., in their study to elucidate the etiology of stroke, showed that D-dimer levels are high in acute, subacute, and chronic periods[18]. Folsom et al. found that high serum basal D-dimer levels are associated with ischemic and cardioembolic stroke[19]. In our study, obstructive CVD was found in 3.13% (n=22) of the newly diagnosed patients.

D-Dimer level increases in renal dysfunction[9]. Gregor Linder et al., in their study on 1305 patients, found that D-dimer levels increased in patients with eGFR<60 mL/min[20]. In our study, chronic renal failure was found in 6.37% (n=97) of D-dimer positive cases.

D-dimer levels increase during normal pregnancy[21]. In a study conducted on healthy pregnant women by measuring

D-dimer levels during the three trimesters, D-dimer levels increased progressively during pregnancy and reached the highest level in the third trimester[22]. In our study, 13 out of 28 pregnant patients were found to have positive D-dimer with no additional pathology.

The specificity of plasma D-dimer levels in the diagnosis of PE is low[9]. Halide Akbaş et al., in their study that D-dimer levels were not effective in predicting hospitalization[12]. However, in our study, although the diagnosis of PE was low in D-dimer positive cases, other diseases requiring hospitalization were found to be significantly higher ($p<0.05$). While the rate of hospitalization to ICU was 17.2% in D-dimer positive patients, this rate was 8.8% in D-dimer negative patients. The clinical hospitalization rate was 23.5% in D-dimer positive patients whreas this rate was 7% in D-dimer negative patients.

**Limitations**

Since our study is retrospective, the lack of some data, such as risk scoring, is the limiting factor for our study.

## Conclusion

D-dimer has a low specifity in the diagnosis of PE. However, other than PE, the rate of patients requiring clinical and especially ICU hospitalization is high in D-dimer positive cases. Therefore, even if PE is not detected in D-dimer positive cases, it is thought that further investigation should be considered having in mind the probability of serious conditions such as malignancy that may not be detected during emergency examination and investigations. There is need for new studies on this subject.

## References


1. Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in context: D-Dimer. J Am Coll Cardiol 2017;70:2411-2420.
2. Keller K, Beule J, Balzer JO, Dippold W. D-Dimer and thrombus burden in acute pulmonary embolism. Am J Emerg Med 2018 ;36:1613-1618.
3. Bass AR, Fields KG, Goto R, Turissini G, Dey S, Russell LA. Clinical decision rules for pulmonary embolism in hospitalized patients: a systematic literature review and meta-analysis. Thromb Haemost 2017;117:2176-2185.
4. Wakai A, Gleeson A, Winter D. Role of fibrin D-dimer testing in emergency medicine. Emerg Med J 2003;20:319–325.
5. Geersing GJ, Janssen KJ, Oudega R, et al. Excluding venous thromboembolism using point of care D-dimer tests in outpatients: a diagnostic meta-analysis. BMJ 2009;339:b2990.
6. Farm M, Siddiqui AJ, Onelöv L, et al. Age-adjusted D-dimer cut-off leads to more efficient diagnosis of venous thromboembolism in the emergency department: a comparison of four assays. J Thromb Haemost 2018;16:866-875.
7. Carrier M, Righini M, Djurabi RK, et al. VIDAS D-dimer in combination with clinical pre-test probability to rule out pulmonary embolism. A systematic review of management outcome studies. Thromb Haemost 2009;101:886-892.
8. den Exter PL, van Es J, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. Blood 2013;122:1144-1149.
9. Kabrhel C, Mark Courtney D, Camargo CA Jr, et al. Factors associated with positive D-dimer results in patients evaluated for pulmonary embolism. Acad Emerg Med 2010;17:589-597.
10. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted D-dimer cutoff levels to rule out pulmonary embolism: the ADJUST-PE study. JAMA 2014;311:1117-1124.
11. Lippi G, Bonfanti L, Saccenti C, Cervellin G. Causes of elevated D-dimer in patients admitted to a large urban emergency department. Eur J Intern Med 2014;25:45-48.
12. Akbaş SH, Can M, Kılıçarslan I, Özdem S, Çete Y, Gültekin M. Acil Servise Başvuran Yüksek D-dimer Düzeyli Hastalarda Tanı Dağılımı ve D-dimer Düzeylerinin Hastaneye Yatış ve Ölüm Oranları ile İlişkisi. Turk J Emerg Med 2004;4:149-154.
13. Falanga A, Russo L, Milesi V, Vignoli A. Mechanisms and risk factors of thrombosis in cancer. Crit Rev Oncol Hematol. 2017;118:79-83.
14. Levitan N, Dowlati A, Remick SC, et al. Rates of initial and recurrent thromboembolic disease among patients with malignancy versus those without malignancy. Risk analysis using Medicare claims data. Medicine 1999;78:285-291.
15. Wang S, Zimmermann S, Parikh K, Mansfield AS, Adjei AA. Current Diagnosis and Management of Small-Cell Lung Cancer. Mayo Clin Proc 2019 ;94:1599-1622.
16. Stein PD, Gottschalk A, Saltzman HA, Terrin ML. Diagnosis of acute pulmonary embolism in the elderly. J Am Coll Cardiol 1991 ;18:1452-1457.
17. Hamatani Y, Nagai T, Nakai M, et al. Elevated plasma d-dimer level is associated with short-term risk of ischemic stroke in patients with acute heart failure. Stroke 2018; 49:1737-1740.
18. Montaner J, Perea-Gainza M, Delgado P et al. Etiologic diagnosis of ischemic stroke subtypes with plasma biomarkers. Stroke 2008;39:2280-2287.
19. Folsom AR, Gottesman RF, Appiah D, Shahar E, Mosley TH. Plasma d-dimer and incident ischemic stroke and coronary heart disease: the atherosclerosis risk in communities study. Stroke 2016;47:18-23.
20. Lindner G, Funk GC, Pfortmueller CA, et al. D-dimer to rule out pulmonary embolism in renal insufficiency. Am J Med 2014 ;127:343-347.
21. Kovac M, Mikovic Z, Rakicevic L, et al. The use of d-dimer with new cutoff can be useful in diagnosis of venous thromboembolism in pregnancy. Eur J Obstet Gynecol Reprod Biol. 2010;148:27-30.
22. Gutiérrez García I, Pérez Cañadas P, Martínez Uriarte J, et al. D-dimer during pregnancy: establishing trimester-specific reference intervals. Scand J Clin Lab Invest 2018;78:439-442.