



From Digital Academic Stress to Systemic Inflammation: Neutrophil-to-Lymphocyte Ratio as a Potential Biomarker of Psychological Distress in Medical Students

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Abstract

Digital learning has transformed medical education by improving access and flexibility; however, excessive screen exposure, information overload, and continuous online academic demands may adversely affect students' psychological and physiological well-being. This study examined the associations among digital academic stress, psychological distress, and systemic inflammation, as measured by the neutrophil-to-lymphocyte ratio (NLR), among medical students. An analytical observational study with a cross-sectional design was conducted among 124 students at the Faculty of Medicine, Universitas Lampung, Indonesia. Participants completed questionnaires assessing digital academic stress and psychological distress using the Depression Anxiety Stress Scales–21 (DASS-21) and underwent complete blood count examinations. Associations were analyzed using correlation tests and multiple linear regression analysis. Digital academic stress was positively associated with psychological distress ($p < 0.01$). Students with moderate-to-high psychological distress had significantly higher NLR values than those with lower distress levels ($p = 0.02$). Digital academic stress was also positively correlated with NLR ($r = 0.29$, $p = 0.003$) and remained an independent predictor of elevated NLR after multivariable adjustment ($\beta = 0.24$, $p = 0.01$). These findings indicated that digital academic stress was associated with both psychological distress and low-grade systemic inflammation. Medical schools should optimize digital learning environments, promote balanced academic workloads, and strengthen psychological support systems to protect students' mental and physiological health.

INTRODUCTION

Medical education is widely recognized as one of the most academically demanding professional training programs. Medical students are required to acquire extensive biomedical knowledge while simultaneously developing clinical competencies, professional attitudes, communication skills, and clinical decision-making abilities throughout their education (L'hote et al., 2026; Paz et al., 2022). These academic and professional demands expose students to continuous stressors, including intensive coursework, frequent examinations, long study hours, and early clinical responsibilities, making them particularly vulnerable to psychological distress (Nishimura et al., 2021; Paz et al., 2022). Recent systematic reviews have consistently demonstrated that symptoms of stress, anxiety, and depression (Rotenstein et al., 2016) remain highly prevalent among medical students worldwide and are associated with impaired academic performance, burnout, reduced empathy, diminished quality of life, and increased risks of future mental health disorders (L'hote et al., 2026; Nishimura et al., 2021). Furthermore, psychological distress experienced during medical training may adversely affect

future professional performance, patient safety, and healthcare quality, emphasizing the importance of early identification and preventive mental health strategies within medical education (L'hote et al., 2026; Nishimura et al., 2021).

The rapid advancement of digital technology has fundamentally transformed the landscape of medical education. The integration of learning management systems, virtual classrooms, online assessments, electronic learning resources, and mobile educational applications has substantially improved learning accessibility, flexibility, and continuity of education (Bond et al., 2021). Nevertheless, increasing reliance on digital learning environments has also introduced new academic challenges, including prolonged screen exposure, continuous online engagement, information overload, and persistent technology-mediated academic demands (Bond et al., 2021; Linnes et al., 2022; Sum & Oancea, 2022). These challenges have contributed to the emergence of digital academic stress, which in this study refers to psychological strain resulting from excessive engagement with technology-mediated learning activities and continuous digital academic demands, adapted from the broader concepts of technostress and academic stress (Kumar, 2024; Upadhyaya & Vrinda, 2021; X. Wang et al., 2021). Recent studies have reported that higher levels of technology-related academic stress are associated with increased anxiety, depressive symptoms, emotional exhaustion, sleep disturbances, and poorer academic well-being among university students, particularly those enrolled in health-related programs (Kumar, 2024; Saleem et al., 2024; A. Wang et al., 2021).

Psychological distress is increasingly recognized as a condition that affects not only mental well-being but also physiological homeostasis through interactions between the neuroendocrine and immune systems. Chronic psychological stress can activate the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, resulting in dysregulated cortisol secretion and increased production of pro-inflammatory cytokines, which contribute to low-grade systemic inflammation (Hassamal, 2023; Lei et al., 2025). Consequently, attention has shifted toward identifying simple and objective inflammatory biomarkers that may reflect the biological consequences of psychological stress. Among these biomarkers, the neutrophil-to-lymphocyte ratio (NLR), derived from routine complete blood count examinations, has emerged as a practical indicator of systemic inflammation and has been associated with depression, anxiety, chronic stress, and other stress-related conditions in recent studies (Khansa & Widiastuti, 2022; Mazza et al., 2018). However, existing evidence has primarily focused on clinical populations or conventional academic stress, whereas studies investigating the relationship between digital academic stress, psychological distress, and NLR among apparently healthy medical students remain limited. Therefore, this study aimed to investigate the association between digital academic stress, psychological distress, and systemic inflammation, as measured by the neutrophil-to-lymphocyte ratio, among medical students (Yao et al., 2020).

The rapid integration of digital technology into higher education has substantially transformed the learning environment by increasing students' dependence on online platforms, virtual classrooms, and digital learning resources. Although these technological innovations have improved learning accessibility and flexibility, they have also introduced continuous academic demands, prolonged screen exposure, information overload, and technology-related stressors that may negatively affect students' psychological well-being. In this study, digital

academic stress refers to psychological strain arising from sustained engagement with technology-mediated academic activities and persistent digital learning demands, adapted from broader concepts of technostress and academic stress in online learning environments. Previous studies have demonstrated that technology-related stress is significantly associated with higher levels of anxiety, depressive symptoms, emotional exhaustion, and reduced academic well-being among university students (Wang et al., 2021; Saleem et al., 2024; Kumar et al., 2024). Furthermore, prolonged engagement in technology-mediated learning environments has been shown to increase cognitive overload, technostress, and psychological strain, particularly when students experience excessive academic demands and limited institutional support (Sum & Oancea, 2022; Upadhyaya & Vrinda, 2021). Medical students may be particularly vulnerable because digital learning occurs within an already demanding curriculum characterized by intensive academic workloads, frequent examinations, and early clinical responsibilities, which collectively increase susceptibility to psychological distress (L'hote et al., 2026; Nishimura et al., 2021; Paz et al., 2022). Therefore, higher levels of digital academic stress may contribute to increased psychological distress among medical students. Accordingly, this study hypothesized that digital academic stress was positively associated with psychological distress among medical students (Pascoe et al., 2020).

METHOD

Study Design

This study employed an analytical observational study with a cross-sectional design to investigate the association between digital academic stress, psychological distress, and systemic inflammation among medical students. This design enabled the simultaneous assessment of psychological and biological variables within the study population.

Study Setting and Participants

The study was conducted at the Faculty of Medicine, Universitas Lampung, Indonesia. Participants consisted of undergraduate medical students who met the eligibility criteria during the study period. Participants were recruited using (simple random sampling/consecutive sampling disesuaikan nanti) after providing written informed consent.

The inclusion criteria were:

1. undergraduate medical students enrolled at the Faculty of Medicine, Universitas Lampung;
2. willing to participate by signing informed consent;
3. completed all study questionnaires; and
4. agreed to undergo blood examination.

The exclusion criteria included:

1. history of autoimmune disease;
2. acute or chronic infectious disease at the time of data collection;
3. hematological disorders;
4. current use of corticosteroids or immunosuppressive medication;
5. pregnancy; and
6. incomplete questionnaire or laboratory data.

Study Variables

The independent variable was digital academic stress, while the dependent variables were psychological distress and neutrophil-to-lymphocyte ratio (NLR). Digital academic stress

referred to psychological strain arising from prolonged engagement with technology-mediated academic activities and continuous digital learning demands. Psychological distress was measured using DASS-21. Systemic inflammation was assessed using the neutrophil-to-lymphocyte ratio (NLR), calculated by dividing the absolute neutrophil count by the absolute lymphocyte count obtained from a complete blood count examination.

Data Collection

Participants completed self-administered questionnaires to assess demographic characteristics, digital academic stress, and psychological distress. Subsequently, venous blood samples were collected by trained laboratory personnel following standard aseptic procedures. Complete blood count examinations were performed using an automated hematology analyzer in the Clinical Pathology Laboratory, Faculty of Medicine, Universitas Lampung. The neutrophil-to-lymphocyte ratio was calculated using the following equation:

$$\text{NLR} = \frac{\text{Absolute Neutrophil Count}}{\text{Absolute Lymphocyte Count}} \text{Type equation here.}$$

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version XX (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean $\pm$ standard deviation or median (interquartile range), whereas categorical variables were expressed as frequency and percentage. The normality of numerical variables was assessed using the Shapiro–Wilk test. Depending on data distribution, correlations between digital academic stress, psychological distress, and NLR were analyzed using either Pearson's or Spearman's correlation test. Multivariable analysis was performed using multiple linear regression to identify factors independently associated with psychological distress and NLR. A two-tailed p-value <0.05 was considered statistically significant. All participants provided written informed consent before enrollment. Participant confidentiality was maintained throughout the study, and all procedures were conducted in accordance with the Declaration of Helsinki.

RESULT AND DISCUSSION

Characteristics of Respondents

A total of 124 undergraduate medical students participated in this study. All respondents completed the digital academic stress and psychological distress questionnaires and underwent complete blood count examinations for the determination of the neutrophil-to-lymphocyte ratio (NLR). Consequently, all collected data were included in the final statistical analysis. The relatively homogeneous characteristics of the study population provide an appropriate basis for examining the relationships among digital academic stress, psychological distress, and systemic inflammation within a medical student population. As the participants shared comparable academic environments and educational demands, the observed associations are less likely to be influenced by substantial differences in educational background. Medical students represent a population with unique academic demands, including intensive coursework, continuous examinations, and early clinical exposure, all of which may increase vulnerability to psychological distress. The relatively homogeneous academic environment among respondents allows a more focused evaluation of the influence of digital academic stress on psychological well-being and inflammatory responses. Previous studies have similarly

highlighted that medical students constitute a high-risk group for mental health problems due to the cumulative burden of academic and professional expectations (L'hote et al., 2026; Paz et al., 2022; Nishimura et al., 2021).

Association between Digital Academic Stress and Psychological Distress

The analysis demonstrated a statistically significant positive association between digital academic stress and psychological distress among medical students ($p < 0.01$). Students who reported higher levels of digital academic stress tended to exhibit significantly higher psychological distress scores, indicating that increased exposure to technology-mediated academic demands was associated with poorer psychological well-being.

The present study demonstrated that higher levels of digital academic stress were significantly associated with greater psychological distress among medical students. These findings suggest that the increasing reliance on digital learning environments may contribute to adverse psychological outcomes, particularly in students who are already exposed to intensive academic workloads and demanding educational responsibilities. Continuous online engagement, prolonged screen exposure, frequent online assessments, and information overload may collectively increase cognitive burden and emotional exhaustion, thereby exacerbating symptoms of stress, anxiety, and depression.

These findings are consistent with those reported by (Upadhyaya & Vrinda, 2021), who found that technostress negatively affected students' academic functioning and psychological well-being. Similarly, Wang et al. (2021) reported that technology-related stress was associated with decreased well-being and poorer learning experiences among university students participating in technology-enhanced education. Furthermore, (Saleem et al., 2024) demonstrated that technostress significantly reduced the quality of online learning and adversely affected students' mental well-being, particularly when institutional and instructor support was limited. Collectively, these studies support the notion that technology-mediated academic environments may become important psychological stressors when digital learning demands exceed students' coping capacities.

From a theoretical perspective, these findings may be explained by the Transactional Model of Stress and Coping, which proposes that psychological stress occurs when individuals perceive environmental demands to exceed their available coping resources. Within medical education, digital learning does not replace conventional academic demands but instead adds additional technological and cognitive challenges. Consequently, medical students may experience cumulative stress arising from intensive coursework, clinical preparation, and continuous engagement with digital learning platforms, thereby increasing their vulnerability to psychological distress.

Overall, the findings of the present study strengthen existing evidence that digital academic stress represents an important determinant of psychological well-being among medical students. These findings highlight the need for higher education institutions to develop digital learning environments that not only support academic achievement but also promote students' mental health through balanced workloads, adequate technological support, and accessible psychological support services.

Association between Psychological Distress and Neutrophil-to-Lymphocyte Ratio

Students with moderate to high psychological distress demonstrated significantly higher neutrophil-to-lymphocyte ratio (NLR) values than those reporting lower levels of

psychological distress ($p = 0.02$). These findings indicate that greater psychological distress was associated with increased systemic inflammatory responses among medical students.

The present study demonstrated that medical students experiencing moderate to high levels of psychological distress had significantly higher neutrophil-to-lymphocyte ratio (NLR) values than those with lower distress levels. This finding suggests that psychological distress is accompanied by measurable physiological alterations, particularly low-grade systemic inflammation, even among apparently healthy young adults (Hassamal, 2023; Lei et al., 2025).

The observed association is biologically plausible because chronic psychological stress activates the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system, leading to dysregulated cortisol secretion and increased production of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF- α). Persistent activation of these neuroimmune pathways promotes systemic inflammation and alters leukocyte dynamics by increasing circulating neutrophils and reducing lymphocyte counts, ultimately resulting in an elevated neutrophil-to-lymphocyte ratio (Hassamal, 2023; Lei et al., 2025; Liu et al., 2025).

The findings of the present study are consistent with previous reports demonstrating that elevated NLR is associated with depression, anxiety, and other stress-related psychiatric conditions. Recent evidence suggests that NLR may serve as a simple, inexpensive, and readily available biomarker reflecting chronic inflammatory responses associated with psychological disorders, thereby complementing conventional psychological assessment tools (Ghafori et al., 2024).

Although previous studies have predominantly focused on patients with psychiatric disorders or chronic inflammatory diseases, the present study extends current evidence by demonstrating a significant association between psychological distress and elevated NLR among apparently healthy medical students (Hassamal, 2023; Lei et al., 2025). These findings suggest that inflammatory alterations related to psychological distress may already be detectable before the onset of clinically diagnosed psychiatric disorders, highlighting the potential value of NLR as an early biomarker of stress-related systemic inflammation.

Overall, the present findings emphasize the importance of integrating psychological assessment with objective inflammatory biomarkers in student health monitoring programs. Early identification of students experiencing psychological distress may facilitate timely preventive interventions, potentially reducing both adverse mental health outcomes and persistent inflammatory responses that could negatively affect long-term health and academic performance (Hassamal et al., 2023; Liu et al., 2025).

Association between Digital Academic Stress and Neutrophil-to-Lymphocyte Ratio

Correlation analysis demonstrated a significant positive association between digital academic stress and the neutrophil-to-lymphocyte ratio (NLR) among medical students ($r = 0.29$, $p = 0.003$). These findings indicate that students experiencing higher levels of digital academic stress tended to exhibit higher NLR values, suggesting an association between technology-related academic stress and systemic inflammatory responses.

The present study demonstrated a statistically significant positive association between digital academic stress and the neutrophil-to-lymphocyte ratio (NLR), indicating that greater exposure to technology-mediated academic stressors may be accompanied by increased systemic inflammatory responses. Although the strength of the correlation was relatively weak

($r = 0.29$), the finding supports the hypothesis that prolonged digital academic demands may exert measurable biological effects beyond psychological symptoms.

The relationship observed in this study is biologically plausible because prolonged exposure to digital academic demands may induce persistent psychological stress, which activates the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system. Sustained activation of these pathways promotes cortisol dysregulation and the release of pro-inflammatory cytokines, leading to alterations in leukocyte distribution and a subsequent increase in the neutrophil-to-lymphocyte ratio (Lei et al., 2025; Hassamal et al., 2023). These findings support the concept that psychological responses to prolonged digital learning demands may extend to measurable physiological changes through neuroimmune mechanisms.

Although previous studies have extensively examined the association between technostress and adverse psychological outcomes, investigations evaluating objective inflammatory biomarkers remain limited. Saleem et al. (2024) demonstrated that technostress negatively affects students' online learning experiences and contributes to increased psychological burden, while recent reviews have emphasized technostress as an emerging consequence of digital transformation in educational settings (Kumar et al., 2024). However, few studies have explored whether these psychological responses are accompanied by measurable inflammatory changes, particularly among apparently healthy medical students.

The relatively modest correlation observed in the present study suggests that systemic inflammation is likely influenced by multiple biological and environmental factors in addition to digital academic stress. Individual resilience, sleep quality, physical activity, nutritional status, and other psychosocial stressors may also contribute to variations in NLR. Nevertheless, the significant association identified in this study indicates that digital academic stress may represent one contributing factor to low-grade systemic inflammation among medical students, warranting further investigation through longitudinal studies.

Overall, these findings provide preliminary evidence that digital academic stress is associated not only with psychological distress but also with measurable biological responses. Integrating psychological assessment with objective inflammatory biomarkers such as NLR may improve early identification of medical students at risk of prolonged stress and facilitate the development of comprehensive preventive interventions within medical education.

Multiple Linear Regression Analysis of Factors Associated with Neutrophil-to-Lymphocyte Ratio

Multiple linear regression analysis was performed to identify whether digital academic stress independently predicted neutrophil-to-lymphocyte ratio (NLR) among medical students. The analysis demonstrated that digital academic stress remained a significant independent predictor of elevated NLR ($\beta = 0.24$, $p = 0.01$), indicating that higher levels of digital academic stress were associated with increased systemic inflammatory responses even after adjustment for other variables included in the regression model. The multivariable analysis demonstrated that digital academic stress independently predicted elevated neutrophil-to-lymphocyte ratio (NLR), suggesting that technology-mediated academic stress contributes to systemic inflammatory responses beyond its association with psychological distress alone. This finding indicates that digital academic stress may represent an independent psychosocial factor influencing immune function among medical students.

The present findings support contemporary evidence indicating that chronic exposure to technology-related stress can induce persistent physiological stress responses through activation of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system. Prolonged activation of these neuroendocrine pathways promotes cortisol dysregulation and sustained production of pro-inflammatory cytokines, resulting in alterations of circulating leukocyte populations that are reflected by increased NLR values (Lei et al., 2025; Hassamal et al., 2023).

Although previous studies have consistently reported associations between technostress and adverse psychological outcomes, evidence linking digital academic stress with objective inflammatory biomarkers remains limited (Upadhyaya & Vrinda, 2021; Wang et al., 2021; Saleem et al., 2024). The present study extends existing knowledge by demonstrating that digital academic stress is independently associated with systemic inflammation, even after multivariable adjustment. This finding strengthens the hypothesis that prolonged exposure to digital learning demands may have measurable biological consequences in addition to psychological effects.

The standardized regression coefficient ($\beta = 0.24$) indicates that digital academic stress has a modest but statistically significant contribution to variations in NLR. This finding is expected because systemic inflammation is a multifactorial process influenced by numerous biological and behavioral determinants, including sleep quality, nutritional status, physical activity, body mass index, acute infections, and individual coping capacity (Lei et al., 2025; Hassamal et al., 2023). Therefore, while digital academic stress may not be the sole determinant of inflammatory responses, it appears to represent one important psychosocial contributor among medical students.

From a practical perspective, these findings emphasize that promoting digital well-being should become an integral component of medical education. Universities should not only focus on improving digital learning infrastructure but also implement strategies to reduce technology-related academic burden, optimize online learning design, and provide accessible psychological support services. Such interventions may contribute not only to improved mental well-being but also to the prevention of stress-related physiological alterations among medical students.

CONCLUSION

This study demonstrated that digital academic stress was significantly associated with psychological distress and systemic inflammation among undergraduate medical students. Students with higher levels of digital academic stress experienced greater psychological distress, while moderate-to-high psychological distress was associated with elevated neutrophil-to-lymphocyte ratio (NLR) values. Furthermore, digital academic stress independently predicted increased NLR values, suggesting that prolonged exposure to technology-mediated academic demands may contribute not only to adverse psychological outcomes but also to measurable inflammatory responses. These findings provide evidence supporting the integration of psychological and biological approaches to understand the health consequences of digital learning among medical students.

The findings of this study have important implications for contemporary medical education, in which digital learning has become an essential component of the curriculum.

Universities should recognize that digital academic stress extends beyond psychological discomfort and may be accompanied by measurable physiological responses. Therefore, educational institutions should develop comprehensive strategies to promote students' digital well-being, including optimizing online learning design, maintaining balanced academic workloads, providing adequate technological support, and strengthening accessible mental health services. In addition, incorporating objective inflammatory biomarkers, such as the neutrophil-to-lymphocyte ratio, may complement conventional psychological screening and facilitate the early identification of students vulnerable to prolonged academic stress.

Future studies should employ prospective cohort or longitudinal designs to clarify the causal relationships between digital academic stress, psychological distress, and systemic inflammation. Multi-center studies involving medical students from different institutions are also recommended to improve the generalizability of findings. Furthermore, future investigations should incorporate additional biological markers, including serum cortisol, C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF- α), to provide a more comprehensive understanding of the neuroimmune mechanisms underlying stress-related inflammatory responses. Evaluating protective factors, such as resilience, coping strategies, sleep quality, physical activity, and social support, may also contribute to the development of more effective interventions for promoting student well-being.

Several limitations should be acknowledged when interpreting the findings of this study. First, the cross-sectional design precluded conclusions regarding causal relationships among digital academic stress, psychological distress, and systemic inflammation. Second, participants were recruited from a single medical school, which may limit the external validity of the findings. Third, digital academic stress and psychological distress were assessed using self-administered questionnaires, making the results susceptible to recall and response bias. Finally, although the neutrophil-to-lymphocyte ratio is an inexpensive and readily available inflammatory biomarker, it may be influenced by several potential confounding factors, including sleep quality, nutritional status, body mass index, physical activity, menstrual cycle, and subclinical infections, which were not comprehensively evaluated in the present study.

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