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Research article

Characteristic profile of platelet indices, neutrophil to lymphocyte ratio, erythrocyte sedimentation rate and homocysteine compared with c-reactive protein in cerebral infarction patients

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1 Figure and 21 References

Key words: Mean platelet volume, Mean platelet volume / platelet count, Neutrophil to lymphocyte ratio, Erythrocyte sedimentation rate, Homocysteine, Cerebral infarction

Abstract

Objective: Elevations of c-reactive protein (CRP) is one of the major acute-phase response following ischemic or hemorrhagic stroke. This study aims to investigate whether platelet indices, neutrophil to lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR), and homocysteine compared with CRP have a clinical importance in cerebral infarction patients.

Setting: The clinical data of cerebral infarction patients were analyzed retrospectively.

Participants: We analyzed unduplicated 516 cerebral infarction patients (Male = 291, Female = 225).

Outcome measures: Hematologic parameters such as mean platelet volume (MPV), Mean platelet volume to platelet count (MPV/PC), NLR, ESR and homocysteine were compared with CRP in cerebral infarction patients in a single institute.

Results: CRP showed significant correlations with MPV/PC ($r = 0.164$, $p<0.001$), NLR ($r = 0.517$, $p<0.001$), and ESR ($r = 0.479$, $p<0.001$) in cerebral infarction patients. MPV or homocysteine did not show a significant correlation with CRP. These results were also noted in male or female divided group analysis.

Conclusions: MPV/PC, NLR, and ESR showed significant correlation with CRP in cerebral infarction patients. MPV/PC, NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer. Further well designed and large scale prospective studies are warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

Strengths and limitations of this study

- Mean platelet volume / Platelet count (MPV/PC) and neutrophil to lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) may be useful parameters for evaluating cerebral infarction patients compared with CRP.
- MPV or NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer.
- Limitations of this study should be considered, including its retrospectively not categorized patients group according to the cerebral infarction type, with or without considering underlying diseases such as diabetes, cardiovascular disease, or chronic inflammatory diseases.
- Further related study would be needed to investigate the meaning of platelet indices and NLR in monitoring of cerebral infarction patients

INTRODUCTION

There have been many efforts to find useful diagnostic biomarkers in cerebral infarction patients. Elevations of c-reactive protein (CRP), the major acute-phase response following ischemic or hemorrhagic stroke are associated with death and vascular complications.[1] Also, erythrocyte sedimentation rate (ESR), a classical acute phase marker was often compared with CRP. As part of those efforts, homocysteine was evaluated in stroke patients.[2 3] Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. There are many mechanisms by which increased homocysteine level could contribute to vascular disease. The principal mechanisms were suggested to involve impaired endothelial function, increased oxidative stress, alterations of lipid metabolism, and induction of thrombosis.[4] Recently, there were a number of reports concerning platelet indices such as mean platelet volume (MPV), and MPV/platelet count (PC) ratio have clinical meanings in various conditions such as atherosclerosis,[5 6] cerebral infarction,[7] or active inflammatory diseases,[8 9] even high MPV was associated with fractures.[10] Also, neutrophil to lymphocyte ratio (NLR) parameter was reported to be an important measure of systemic inflammation.[11] However, the platelet indices or NLR have not been fully investigated to role as a useful surrogate biomarker of diagnosis of cerebral infarction patients. This study aims to show whether platelet indices, NLR, ESR, and homocysteine compared with CRP have a clinical importance in cerebral infarction patients.

METHODS

Retrospectively, we analyzed unduplicated 516 cerebral infarction patients (age mean: 66.2±12.7, male to female ratio: 1.3 (291 to 225)) whose mean platelet volume (MPV), MPV/PC ratio, NLR, ESR, and homocysteine were compared with CRP from January 2010 to September 2013. All patients' medical data were ethically protected and were solitary analyzed for this retrospective study. CRP levels were measured by HiSens hsCRP LTIA (HBI Co., Ltd., Anyang, Korea) as read on the TBA-200FR NEO automated clinical chemistry analyzer (Toshiba Medical Systems Corporation, Tochigi-ken, Japan). PC, MPV, and NLR were measured by Beckman Coulter LH 750 or 780 (Beckman Coulter, Miami, USA) hematology analyzers. ESR was measured by TEST 1 (Alifax, Padova, Italy), a closed automated analyzer determines the ESR which uses the aggregation capacity of RBCs by telemetry.[12] Homocysteine was measured by Hisens Homocysteine (HBI Co., Ltd, Anyang, Korea) using TBA-200 FR NEO automatic chemistry analyzer (Toshiba Medical Systems Corporation, Tochigi-ken, Japan). Statistically, the correlation analysis of the two parameters was performed by using the Pearson correlation test. A *p*-value of less than 0.05 was considered significant. Statistical analyses were performed using IBM SPSS Statistics Version 20 (IBM Corporation, Armonk, NY).

RESULTS

CRP showed significant correlations with MPV/PC (r = 0.164, $p<0.001$), NLR (r = 0.517, $p<0.001$), and ESR (r = 0.479, $p<0.001$) in cerebral infarction patients (figure 1). However, there was not a significant correlation between CRP and MPV (r = 0.068, p = 0.121), or between CRP and homocysteine (r = 0.026, p = 0.555) in cerebral infarction patients. Also, these similar results were noted in male (n = 291) or female (n = 225) divided group analysis.

In male group, CRP showed significant correlations with MPV/PC (r = 144, p = 0.014), NLR (r = 0.413, p<0.001), and ESR (r = 0.82, p<0.001) in cerebral infarction patients. In female group, CRP showed significant correlations with MPV/PC (r = 0.197, p = 0.003), NLR (r = 0.620, p<0.001), and ESR (r = 0.484, p<0.001) in cerebral infarction patients.

DISCUSSION

There was many considering factors of cerebral infarction pathogenesis. We thought activated platelet could be produced in various cerebral vascular diseases and these conditions might increase MPV. Of the many pathogenesis, we think that inflammation has a critical role on cerebral infarction. Inflammation is found to develop at a sufficiently early stage in progressive ischemic brain injury.[13] A positive correlation of C-reactive protein (CRP) with MPV/PC, and NLR were noted in our another study.[14] Recently, there were various studies which dealt with relationship between hematologic indices and cerebral infarction.[15 16 17] Arikanoglu et al. reported that CRP and MPV are higher in the ischemic stroke patients who died in comparison to those who survived.[15] MPV is a novel index for silent cerebral infarction regardless of classical cardiovascular risk factors.[16] Also, NLR predicts poor prognosis in ischemic cerebrovascular disease.[17] Although, CRP level and outcome of ischemic stroke is under debated,[18] the inflammation might be related with of certain progression of cerebral infarction. Therefore, CRP, representative inflammatory marker, it seems to be useful to compare new parameters with CRP in cerebral infarction patients.

For the first time, this study showed MPV/PC and NLR as expected ESR could be statistically correlated with CRP in cerebral infarction patients in large population group

without gender difference. The present study might support further related studies dealt with an association between cerebral infarction and inflammation. Also, MPV/PC and NLR should be further investigated to have a clinical impact of disease progression and expectation of mortality in cerebral infarction patients. Up to date, the consensus diagnostic cut-off ranges of MPV/PC, and NLR has not been established for evaluation of cerebral infarction. Also, platelet indices measures the femto-liter (10^{-15} L) levels and still has not been standardized and it showed the result variations within device to device.[19] This study has some internal limitations that we retrospectively analyzed patients group for a long time. We did not categorize specific cerebral infarction types and strictly exclude patients with additional disease such as diabetes, cardiovascular diseases, malignant diseases might impact level of enrolled parameters. In addition, we could not strictly exclude delayed analyzed specimens. MPV can be influenced by the time interval between sampling and analysis.[20] MPV results become increasingly unreliable after 4 hours.[21] Complete blood count (CBC) analysis in our laboratory has been almost proceeded within 4 hours from sampling start.

In conclusion, we newly suggested a possibility of MPV/PC and NLR may be useful parameters for evaluating cerebral infarction patients compared with CRP. Characteristically, MPV or NLR are inexpensive and simple parameters can be attainable by automatic hematology analyzer. Therefore, further well designed and large scale prospective studies are warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

Contributors

Jong-Han Lee designed and participated in all stages of the study. Kyum-Yil Kwon consulted diagnosis of patients. Soo Young Yoon, Hyon-Suk Kim and Chae Seung Lim helped to consultations of this study.

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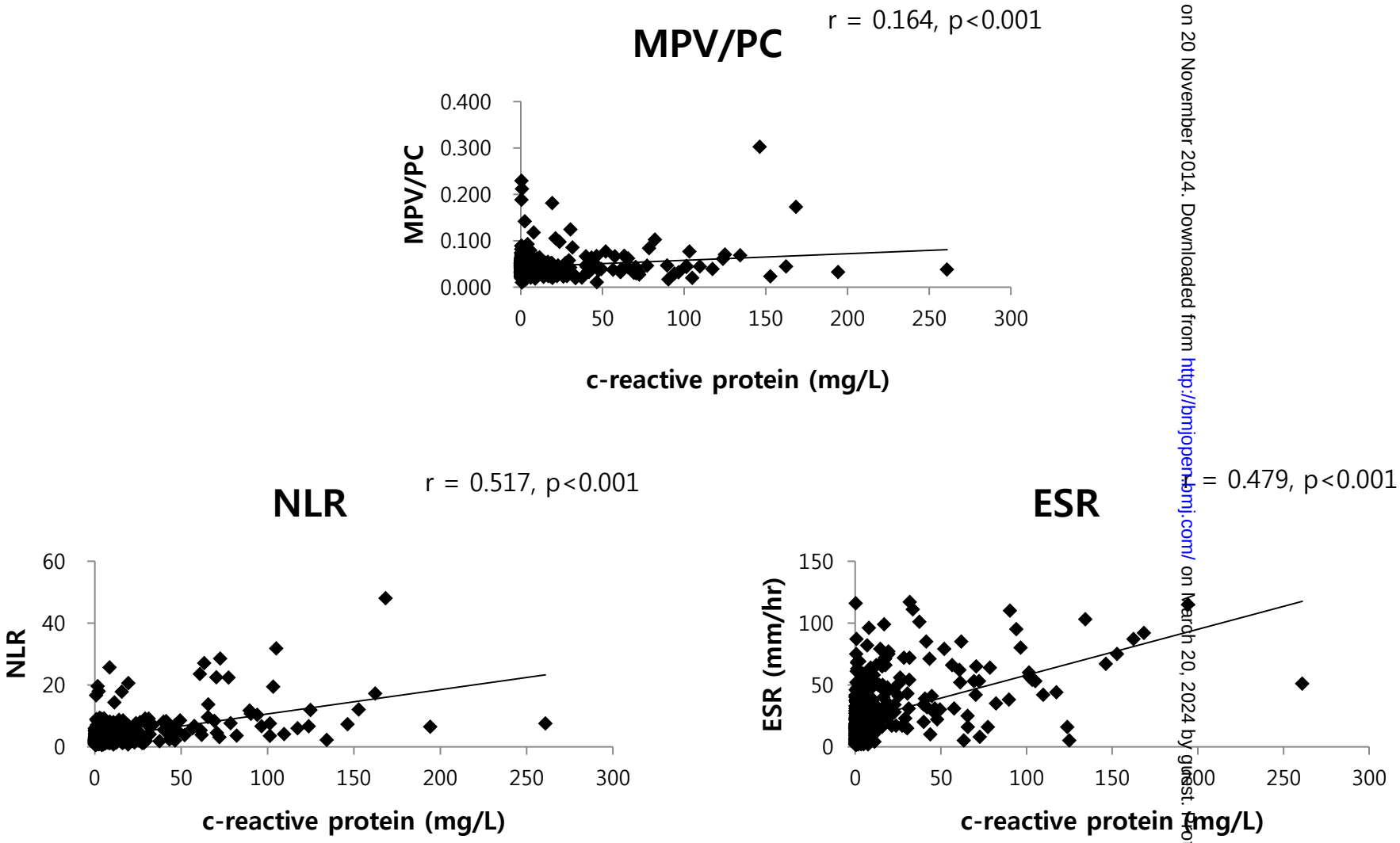

Figure 1 Correlation analysis between c-reactive protein and MPV/PC, NLR, and ESR

Abbreviation: MPV, mean platelet volume; PC, platelet count; NLR, neutrophil to lymphocyte ratio; ESR, erythrocyte sedimentation rate; r, Pearson correlation coefficient.

STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1-2
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	4
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	4-5
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	5
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	N/A
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	5
Test methods	7	The reference standard and its rationale.	N/A
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	5
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	N/A
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	N/A
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	N/A
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	4-5
	13	Methods for calculating test reproducibility, if done.	N/A
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	5
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	5
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	N/A
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	N/A
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	N/A
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A
	20	Any adverse events from performing the index tests or the reference standard.	N/A
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	N/A
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	5-6
	24	Estimates of test reproducibility, if done.	N/A
DISCUSSION	25	Discuss the clinical applicability of the study findings.	6-7

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Research article

Characteristics of platelet indices, neutrophil to lymphocyte ratio and erythrocyte sedimentation rate compared with c-reactive protein in cerebral infarction patients

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1 Figure and 27 References

Key words: Mean platelet volume, Mean platelet volume/platelet count, Neutrophil to lymphocyte ratio, Erythrocyte sedimentation rate, Cerebral infarction

Abstract

Objective: Elevation of c-reactive protein (CRP) is one of the major acute-phase response following ischemic or hemorrhagic stroke. This study aims to investigate the associations between platelet indices, neutrophil to lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) compared with CRP in cerebral infarction patients.

Setting: The clinical data of cerebral infarction patients were analyzed retrospectively.

Participants: We analyzed unduplicated 516 cerebral infarction patients (mean age: 66.2±12.7, Male /Female= 291/225).

Outcome measures: Mean platelet volume (MPV), mean platelet volume to platelet count (MPV/PC), NLR and ESR were compared with CRP in cerebral infarction patients in a single institute through Spearman correlation test.

Results: There were significant correlations between CRP and MPV ($\rho = 0.088$, $p = 0.045$), NLR ($r = 0.4$, $p<0.001$), and ESR ($r = 0.468$, $p<0.001$) in cerebral infarction patients. In male group, NLR ($\rho = 0.398$, $p<0.001$) and ESR ($\rho = 0.502$, $p<0.001$) showed significant correlations with CRP. In female group, CRP showed significant correlations with MPV ($\rho = 0.17$, $p = 0.011$), NLR ($\rho = 0.392$, $p<0.001$), and ESR ($\rho = 0.475$, $p<0.001$).

Conclusions: MPV, NLR, and ESR showed significant correlation with CRP in cerebral infarction patients. MPV, NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer. Further well designed and large scale prospective studies are warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

Strengths and limitations of this study

- Mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) were positively associated with c-reactive protein (CRP) in cerebral infarction patients, especially female patients.
- MPV, NLR and ESR may be useful parameters for evaluating cerebral infarction patients compared with CRP.
- MPV or NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer.
- Further well designed studies are warranted to understand the exact meaning of platelet indices and NLR in monitoring of cerebral infarction patients

INTRODUCTION

There have been many efforts to find useful diagnostic markers for monitoring cerebral infarction patients. C-reactive protein (CRP) is a marker of inflammation and a hallmark of the acute-phase response.[1] Many reports suggested that CRP was associated with risk of stroke,[2-4] whereas, some report did not find significant relations.[5 6] Recently, Liu et al. reported that higher high sensitivity-CRP (hs-CRP) concentrations were associated with a higher risk of ischemic stroke, particularly for non-fatal stroke, male and hypertensive subjects but there were no significant associations between hs-CRP and intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH) in a large prospective study.[7] Also, erythrocyte sedimentation rate (ESR), a classical acute phase marker was often compared with CRP. Recently, there were a number of reports dealt with platelet indices such as mean platelet volume (MPV), and MPV/platelet count (PC) ratio have clinical meanings in various conditions such as atherosclerosis,[8 9] cerebral infarction,[10] or active inflammatory diseases,[11 12] even high MPV was associated with fractures.[13] Also, neutrophil to lymphocyte ratio (NLR) parameter was reported to be an important measure of systemic inflammation.[14] However, the platelet indices or NLR have not been fully investigated to role as a useful surrogate biomarker of diagnosis of cerebral infarction patients. This study aims to show any association between platelet indices, NLR and ESR compared with CRP in cerebral infarction patients.

METHODS

Data extraction

Retrospectively, we analyzed unduplicated 516 cerebral infarction patients (mean age:

66.2±12.7 year, male to female ratio: 1.3 (291 to 225)) whose MPV, MPV/PC ratio, NLR and ESR were compared with CRP from January 2010 to September 2013. All patients' medical data were ethically protected and were solitary analyzed for this retrospective study. CRP levels were determined by HiSens hsCRP LTIA (HBI Co., Ltd., Anyang, Korea), latex-enhanced turbidimetric immunoassay, as read on the TBA-200FR NEO automated clinical chemistry analyzer (Toshiba Medical Systems Corporation, Tochigi-ken, Japan). PC, MPV, and NLR were measured by Beckman Coulter LH 750 or 780 (Beckman Coulter, Miami, USA) hematology analyzers. ESR was measured by TEST 1 (Alifax, Padova, Italy), a closed automated analyzer determines the ESR which uses the aggregation capacity of RBCs by telemetry.[15]

Statistical analysis

All data were confirmed by using Kolmogorov-Smirnov test and Shapiro-Wilk test for identifying normal distribution. The correlation analysis of the two parameters was performed by using the Spearman correlation analysis when normal distribution was not confirmed and Pearson correlation test was used when variables were normally distributed. A *p*-value of less than 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics Version 20 (IBM Corporation, Armonk, NY).

RESULTS

The analyzed parameters were not normally distributed ($p<0.05$), therefore we trusted Spearman correlation analysis. CRP showed significant correlations with MPV ($\rho = 0.088$, $p = 0.045$), NLR ($\rho = 0.4$, $p<0.001$), and ESR ($\rho = 0.468$, $p<0.001$) in cerebral infarction

patients (figure 1). However, MPV/PC (ρ = 0.016, p = 0.711) was not significantly correlated with CRP in cerebral infarction patients. In male group (n = 291), CRP showed significant correlations with NLR (ρ = 0.398, p<0.001), and ESR (ρ = 0.502, p<0.001) in cerebral infarction patients. However, MPV (ρ = 0.008, p = 0.890) and MPV/PC (ρ = -0.077, p = 0.188) were not significantly correlated with CRP in male group. In female group (n = 225), CRP showed significant correlations with MPV (ρ = 0.17, p = 0.011), NLR (ρ = 0.392, p<0.001), and ESR (ρ = 0.475, p<0.001) in cerebral infarction patients. However, MPV/PC was not significantly correlated with CRP (ρ = 0.104, p=0.121) in female group.

Although analyzed parameters were not normally distributed, if Pearson correlation test used, CRP showed significant correlations with MPV/PC (r = 0.164, p<0.001), NLR (r = 0.517, p<0.001), and ESR (r = 0.479, p<0.001) in cerebral infarction patients. However, there was not a significant correlation between CRP and MPV (r = 0.068, p = 0.121) in cerebral infarction patients. Also, these similar results were noted in male (n = 291) or female (n = 225) divided group analysis. In male group, CRP showed significant correlations with MPV/PC (r = 144, p = 0.014), NLR (r = 0.413, p<0.001), and ESR (r = 0.82, p<0.001) in cerebral infarction patients. In female group, CRP showed significant correlations with MPV/PC (r = 0.197, p = 0.003), NLR (r = 0.620, p<0.001), and ESR (r = 0.484, p<0.001) in cerebral infarction patients.

DISCUSSION

There were many factors of cerebral infarction pathogenesis. We thought activated platelet could be produced in various cerebral vascular diseases and these conditions might increase

MPV. The inflammation seems to be related with the pathogenesis of cerebral infarction. Inflammation is found to develop at a sufficiently early stage in progressive ischemic brain injury.[16] Besides cerebral infarction, our previous study showed a positive correlation of C-reactive protein (CRP) with MPV/PC, and NLR were noted in pneumonia patients.[17] Recently, there were various studies which dealt with relationship between hematologic indices and cerebral infarction.[18- 20]

Arikanoglu et al. reported that CRP and MPV are higher in the ischemic stroke patients who died in comparison to those who survived.[18] MPV is a novel index for silent cerebral infarction regardless of classical cardiovascular risk factors.[19] Also, NLR predicts poor prognosis in ischemic cerebrovascular disease.[20] Although, CRP level and outcome of ischemic stroke is under debated,[21] the inflammation might be related with of certain progression of cerebral infarction. Therefore, CRP is one of representative inflammatory marker, it seems to be useful to compare new parameters with CRP in cerebral infarction patients.

For the first time, this study showed MPV and NLR as expected ESR could be statistically correlated with CRP in moderate number of cerebral infarction patients. We identified MPV was correlated with CRP in overall and female group, but was not correlated in male group. A report suggested that women had a higher median platelet count than men in Korea.[22] A few studies suggested that men had slightly higher MPV than women.[23] [24] Only female MPV showed significant correlation with CRP. The exact causes of gender difference were not uncovered but it might be caused from a difference of platelet count or hormone differences between women and men. In Pearson correlation analysis, CRP showed significant correlations with MPV/PC ($r = 0.164$, $p<0.001$), NLR ($r = 0.517$, $p<0.001$), and ESR ($r =$

0.479, p<0.001) in cerebral infarction patients. However, all analyzed parameters were not normally distributed, we considered it is proper to interpret data by Spearman correlation test. Both NLR and ESR were positively correlated with CRP in Pearson or Spearman correlation tests.

This study might support further related studies dealt with an association between cerebral infarction and inflammation. Also, MPV, NLR and ESR should be further investigated to have a clinical impact of disease progression and expectation of mortality in cerebral infarction patients. Up to date, the consensus diagnostic cut-off ranges of MPV and NLR has not been established for evaluation of cerebral infarction. Furthermore, platelet indices measures the femto-liter (10^{-15} L) levels and still has not been standardized and it showed the result variations within device to device.[25] This study has some limitations such as we retrospectively analyzed patients group for quite a long time (3 years and 8 months). We did not categorize specific cerebral infarction types and did not strictly exclude patients with additional disease such as diabetes, cardiovascular diseases, malignant diseases might impact level of enrolled parameters. In addition, MPV can be influenced by the time interval between sampling and analysis.[26] MPV results become increasingly unreliable after 4 hours.[27] Complete blood count (CBC) analysis in our laboratory has been almost proceeded within 2 hours from sampling start.

In conclusion, we newly suggested a possibility of MPV and NLR may be useful parameters for evaluating cerebral infarction patients compared with CRP. Characteristically, MPV or NLR are inexpensive and simple parameters can be attainable by automatic hematology analyzer. Therefore, further well designed and large scale prospective studies are warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

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Research article

Characteristics ~~profile~~ of platelet indices, neutrophil to lymphocyte ratio and , erythrocyte sedimentation rate ~~and homocysteine~~ compared with c-reactive protein in cerebral infarction patients

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1 Figure and 27~~21~~ References

Abstract

Objective: Elevations of c-reactive protein (CRP) is one of the major acute-phase response following ischemic or hemorrhagic stroke. This study aims to investigate the associations betweenwhether platelet indices, neutrophil to lymphocyte ratio (NLR) and , erythrocyte sedimentation rate (ESR), and homocysteine compared with CRP have a clinical importance in cerebral infarction patients.

Setting: The clinical data of cerebral infarction patients were analyzed retrospectively.

Participants: We analyzed unduplicated 516 cerebral infarction patients (mean age: 66.2±12.7, (Male /= 291, Female= 291/= 225).

Outcome measures: Mean platelet volume (MPV), Hematologic parameters such as mean platelet volume (MPV), Mean platelet volume to platelet count (MPV/PC), NLR, ESR and ESRhomocysteine were compared with CRP in cerebral infarction patients in a single institute through Spearman correlation test. .

Results: There were significant correlations between CRP and showed significant correlations with MPV (ρ/PC (r = 0.088,0.164, p = 0.045), <0.001), NLR (r = 0.4,0.517, p<0.001), and ESR (r = 0.468,0.479, p<0.001) in cerebral infarction patients. In MPV or homocysteine did not show a significant correlation with CRP. These results were also noted in male group, NLR (ρ = 0.398, p<0.001) and ESR (ρ = 0.502, p<0.001) showed significant correlations with CRP. Inor female group, CRP showed significant correlations with MPV (ρ = 0.17, p = 0.011), NLR (ρ = 0.392, *p*<0.001), and ESR (ρ = 0.475, *p*<0.001).divided group analysis.

Conclusions: MPV,~~MPV/PC,~~ NLR, and ESR showed significant correlation with CRP in cerebral infarction patients. MPV,~~MPV/PC,~~ NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer. Further well designed and large scale prospective studies are warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

Key words: Mean platelet volume, Mean platelet volume/~~ /~~platelet count, Neutrophil to lymphocyte ratio, Erythrocyte sedimentation rate,~~ Homocysteine,~~ Cerebral infarction

Strengths and limitations of this study

- Mean platelet volume (MPV),~~ Platelet count (MPV/PC) and~~ neutrophil to lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) were positively associated with c-reactive protein (CRP) in cerebral infarction patients, especially female patients.
- MPV, NLR and ESR may be useful parameters for evaluating cerebral infarction patients compared with CRP.
- MPV or NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer.
- ~~-~~Further well designed studies are warranted to understand the exact~~Limitations of this study should be considered, including its retrospectively not categorized patients group according to the cerebral infarction type, with or without considering underlying diseases such as diabetes, cardiovascular disease, or chronic inflammatory diseases.~~

- ~~Further related study would be needed to investigate the~~ meaning of platelet indices and NLR in monitoring of cerebral infarction patients

INTRODUCTION

There have been many efforts to find useful diagnostic markers for monitoring cerebral infarction patients. C-reactive protein (CRP) is a marker of inflammation and a hallmark of the acute-phase response.[1] Many reports suggested that CRP was associated with risk of stroke,[2-4] whereas, some report did not find significant relations.[5-6] Recently, Liu et al. reported that higher high sensitivity-CRP (hs-CRP) concentrations were associated with a higher risk of ischemic stroke, particularly for non-fatal stroke, male and hypertensive subjects but there were no significant associations between hs-CRP and intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH) in a large prospective study.[7] Also, erythrocyte sedimentation rate (ESR), a classical acute phase marker was often compared with CRP. Recently, there were a number of reports dealt with platelet indices such as mean

platelet volume (MPV), and MPV/platelet count (PC) ratio have clinical meanings in various conditions such as atherosclerosis,[8 9] cerebral infarction,[10] or active inflammatory diseases,[11 12] even high MPV was associated with fractures.[13] Also, neutrophil to lymphocyte ratio (NLR) parameter was reported to be an important measure of systemic inflammation.[14] However, the platelet indices or NLR have not been fully investigated to role as a useful surrogate biomarker of diagnosis of cerebral infarction patients. This study aims to show any association between platelet indices, NLR and ESR compared with CRP~~biomarkers in cerebral infarction patients. Elevations of c-reactive protein (CRP), the major acute phase response following ischemic or hemorrhagic stroke are associated with death and vascular complications.[1] Also, erythrocyte sedimentation rate (ESR), a classical acute phase marker was often compared with CRP. As part of those efforts, homocysteine was evaluated in stroke patients.[2 3] Homocysteine is an intermediary amino acid formed by the conversion of methionine to cysteine. There are many mechanisms by which increased homocysteine level could contribute to vascular disease. The principal mechanisms were suggested to involve impaired endothelial function, increased oxidative stress, alterations of lipid metabolism, and induction of thrombosis.[4] Recently, there were a number of reports concerning platelet indices such as mean platelet volume (MPV), and MPV/platelet count (PC) ratio have clinical meanings in various conditions such as atherosclerosis,[5 6] cerebral infarction,[7] or active inflammatory diseases,[8 9] even high MPV was associated with fractures.[10] Also, neutrophil to lymphocyte ratio (NLR) parameter was reported to be an important measure of systemic inflammation.[11] However, the platelet indices or NLR have not been fully investigated to role as a useful surrogate biomarker of diagnosis of cerebral infarction patients. This study aims to show whether platelet indices, NLR, ESR, and homocysteine compared with CRP have a clinical importance~~ in cerebral infarction patients.

METHODS

Data extraction

Retrospectively, we analyzed unduplicated 516 cerebral infarction patients ((~~age~~ mean age: 66.2±12.7 year, male to female ratio: 1.3 (291 to 225)) whose MPV,~~mean platelet volume (MPV),~~ MPV/PC ratio, NLR~~, ESR,~~ and ESR~~homocysteine~~ were compared with CRP from January 2010 to September 2013. All patients' medical data were ethically protected and were solitary analyzed for this retrospective study. CRP levels were determined~~measured~~ by HiSens hsCRP LTIA (HBI Co., Ltd., Anyang, Korea), latex-enhanced turbidimetric immunoassay, as read on the TBA-200FR NEO automated clinical chemistry analyzer (Toshiba Medical Systems Corporation, Tochigi-ken, Japan). PC, MPV, and NLR were measured by Beckman Coulter LH 750 or 780 (Beckman Coulter, Miami, USA) hematology analyzers. ESR was measured by TEST 1 (Alifax, Padova, Italy), a closed automated analyzer determines the ESR which uses the aggregation capacity of RBCs by telemetry.[15]

Statistical analysis

All data were confirmed[12] ~~Homocysteine was measured~~ by ~~Hisens Homocysteine (HBI Co., Ltd, Anyang, Korea)~~ using Kolmogorov-Smirnov test and Shapiro-Wilk test for identifying normal distribution. The~~TBA 200 FR NEO automatic chemistry analyzer (Toshiba Medical Systems Corporation, Tochigi ken, Japan). Statistically, the~~ correlation analysis of the two parameters was performed by using the Spearman correlation analysis when normal distribution was not confirmed and Pearson correlation test was used when variables were normally distributed.~~-~~ A *p*-value of less than 0.05 was considered statistically significant.

Statistical analyses were performed using IBM SPSS Statistics Version 20 (IBM Corporation, Armonk, NY).

RESULTS

The analyzed parameters were not normally distributed ($p<0.05$), therefore we trusted Spearman correlation analysis. CRP showed significant correlations with MPV ($\rho = 0.088$, $p = 0.045$), NLR ($\rho = 0.4$, $p<0.001$), and ESR ($\rho = 0.468$, $p<0.001$) in cerebral infarction patients (figure 1). However, MPV/PC ($\rho = 0.016$, $p = 0.711$) was not significantly correlated with CRP in cerebral infarction patients. In male group (n = 291), CRP showed significant correlations with NLR ($\rho = 0.398$, $p<0.001$), and ESR ($\rho = 0.502$, $p<0.001$) in cerebral infarction patients. However, MPV ($\rho = 0.008$, $p = 0.890$) and MPV/PC ($\rho = -0.077$, $p = 0.188$) were not significantly correlated with CRP in male group. In female group (n = 225), CRP showed significant correlations with MPV ($\rho = 0.17$, $p = 0.011$), NLR ($\rho = 0.392$, $p<0.001$), and ESR ($\rho = 0.475$, $p<0.001$) in cerebral infarction patients. However, MPV/PC was not significantly correlated with CRP ($\rho = 0.104$, $p=0.121$) in female group.

Although analyzed parameters were not normally distributed, if Pearson correlation test used, CRP showed significant correlations with MPV/PC ($r = 0.164$, $p<0.001$), NLR ($r = 0.517$, $p<0.001$), and ESR ($r = 0.479$, $p<0.001$) in cerebral infarction patients. ~~(figure 1).~~ However, there was not a significant correlation between CRP and MPV ($r = 0.068$, $p = 0.121$)~~, or between CRP and homocysteine ($r = 0.026$, $p = 0.555$)~~ in cerebral infarction patients. Also, these similar results were noted in male (n = 291) or female (n = 225) divided group analysis. In male group, CRP showed significant correlations with MPV/PC ($r = 144$, $p = 0.014$), NLR

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(r = 0.413, p<0.001), and ESR (r = 0.82, p<0.001) in cerebral infarction patients. In female group, CRP showed significant correlations with MPV/PC (r = 0.197, p = 0.003), NLR (r = 0.620, p<0.001), and ESR (r = 0.484, p<0.001) in cerebral infarction patients.

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DISCUSSION

There were many factors of cerebral infarction pathogenesis. We thought activated platelet could be produced in various cerebral vascular diseases and these conditions might increase MPV. The inflammation seems to be related with the pathogenesis of cerebral infarction. Inflammation is found to develop at a sufficiently early stage in progressive ischemic brain injury.[16] Besides cerebral infarction, our previous study showed a positive correlation of C-reactive protein (CRP) with MPV/PC, and NLR were noted in pneumonia patients.[17] Recently, there were various studies which dealt with relationship between hematologic indices and cerebral infarction.[18 19 20]

Arikanoglu et al. reported that CRP and MPV are higher in the ischemic stroke patients who died in comparison to those who survived.[18] MPV is a novel index for silent cerebral infarction regardless of classical cardiovascular risk factors.[19] Also, NLR predicts poor prognosis in ischemic cerebrovascular disease.[20] Although, CRP level and outcome of ischemic stroke is under debated,[21] the inflammation might be related with of certain progression of cerebral infarction. Therefore, CRP is one of representative inflammatory marker, it seems to be useful to compare new parameters with CRP in cerebral infarction patients.

For the first time, this study showed MPV~~There was many considering factors of cerebral~~

~~infarction pathogenesis. We thought activated platelet could be produced in various cerebral vascular diseases and these conditions might increase MPV. Of the many pathogenesis, we think that inflammation has a critical role on cerebral infarction. Inflammation is found to develop at a sufficiently early stage in progressive ischemic brain injury.[13] A positive correlation of C-reactive protein (CRP) with MPV/PC, and NLR were noted in our another study.[14] Recently, there were various studies which dealt with relationship between hematologic indices and cerebral infarction.[15 16 17] Arikanoglu et al. reported that CRP and MPV are higher in the ischemic stroke patients who died in comparison to those who survived.[15] MPV is a novel index for silent cerebral infarction regardless of classical cardiovascular risk factors.[16] Also, NLR predicts poor prognosis in ischemic cerebrovascular disease.[17] Although, CRP level and outcome of ischemic stroke is under debated,[18] the inflammation might be related with of certain progression of cerebral infarction. Therefore, CRP, representative inflammatory marker, it seems to be useful to compare new parameters with CRP in cerebral infarction patients.~~

~~For the first time, this study showed MPV/PC~~ and NLR as expected ESR could be statistically correlated with CRP in moderate number of cerebral infarction patients. We identified MPV was correlated with CRP in overall and female~~large population~~ group, but was not correlated in male group. A report suggested that women had a higher median platelet count than men in Korea.[22] A few studies suggested that men had slightly higher MPV than women.[23 24] Only female MPV showed significant correlation with CRP. The exact causes of ~~without~~ gender difference were not uncovered but it might be caused from a difference of platelet count or hormone differences between women and men. In Pearson correlation analysis, CRP showed significant correlations with MPV/PC ($r = 0.164$, $p<0.001$), NLR ($r =$

0.517, p<0.001), and ESR (r = 0.479, p<0.001) in cerebral infarction patients. However, all analyzed parameters were not normally distributed, we considered it is proper to interpret data by Spearman correlation test. Both NLR and ESR were positively correlated with CRP in Pearson or Spearman correlation tests.

This~~. The present~~ study might support further related studies dealt with an association between cerebral infarction and inflammation. Also, MPV, NLR~~MPV/PC~~ and ESR~~NLR~~ should be further investigated to have a clinical impact of disease progression and expectation of mortality in cerebral infarction patients. Up to date, the consensus diagnostic cut-off ranges of MPV~~/PC,~~ and NLR has not been established for evaluation of cerebral infarction. Furthermore,~~Also,~~ platelet indices measures the femto-liter (10^{-15} L) levels and still has not been standardized and it showed the result variations within device to device.[25~~19~~] This study has some ~~internal~~ limitations such as ~~that~~ we retrospectively analyzed patients group for quite a long time (3 years and 8 months).~~-~~ We did not categorize specific cerebral infarction types and did not strictly exclude patients with additional disease such as diabetes, cardiovascular diseases, malignant diseases might impact level of enrolled parameters. In addition, ~~we could not strictly exclude delayed analyzed specimens.~~ MPV can be influenced by the time interval between sampling and analysis.[26~~20~~] MPV results become increasingly unreliable after 4 hours.[27~~21~~] Complete blood count (CBC) analysis in our laboratory has been almost proceeded within 24~~4~~ hours from sampling start.

In conclusion, we newly suggested a possibility of MPV~~/PC~~ and NLR may be useful parameters for evaluating cerebral infarction patients compared with CRP. Characteristically, MPV or NLR are inexpensive and simple parameters can be attainable by automatic hematology analyzer. Therefore, further well designed and large scale prospective studies are

warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

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Contributors

Jong-Han Lee designed and participated in all stages of the study. Kyum-Yil Kwon consulted diagnosis of patients. Soo Young Yoon, Hyon-Suk Kim and Chae Seung Lim helped to consultations of this study.

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None

Competing interests

None.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

No additional data are available.

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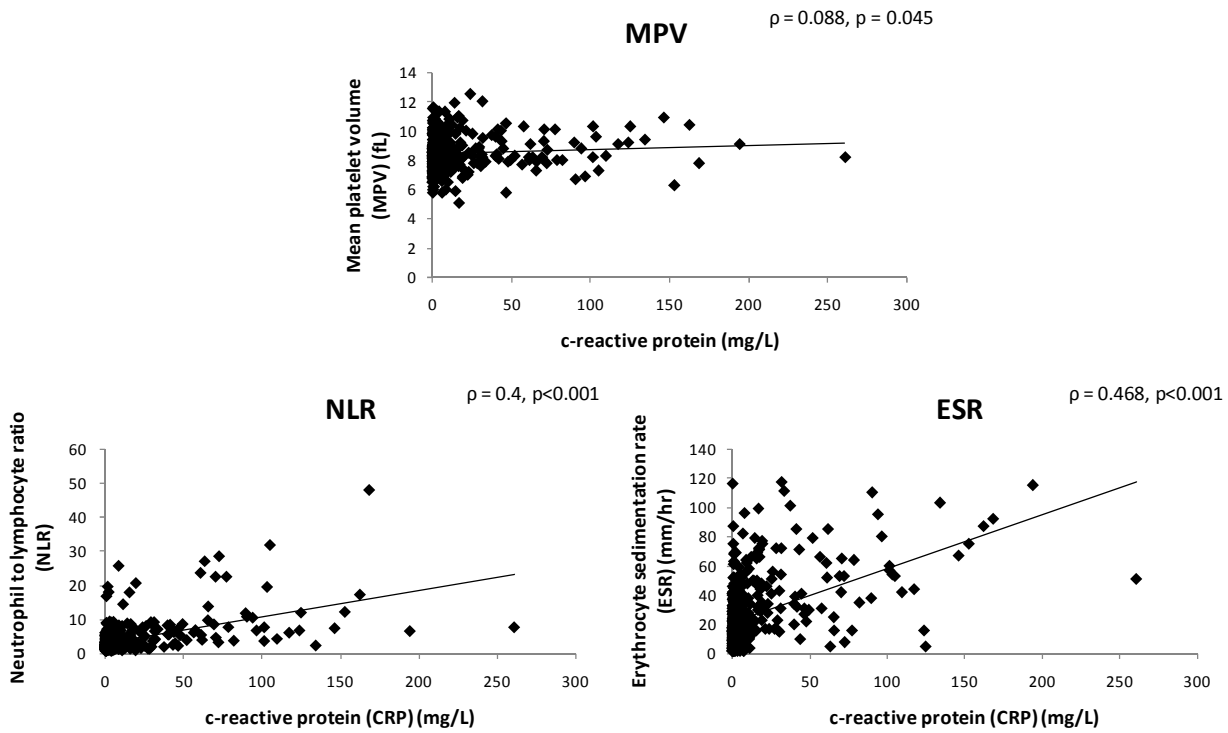

Figure 1. The correlation between mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) in cerebral infraction patients~~1. Di Napoli M, Elkind MS, Godoy DA, *et*~~

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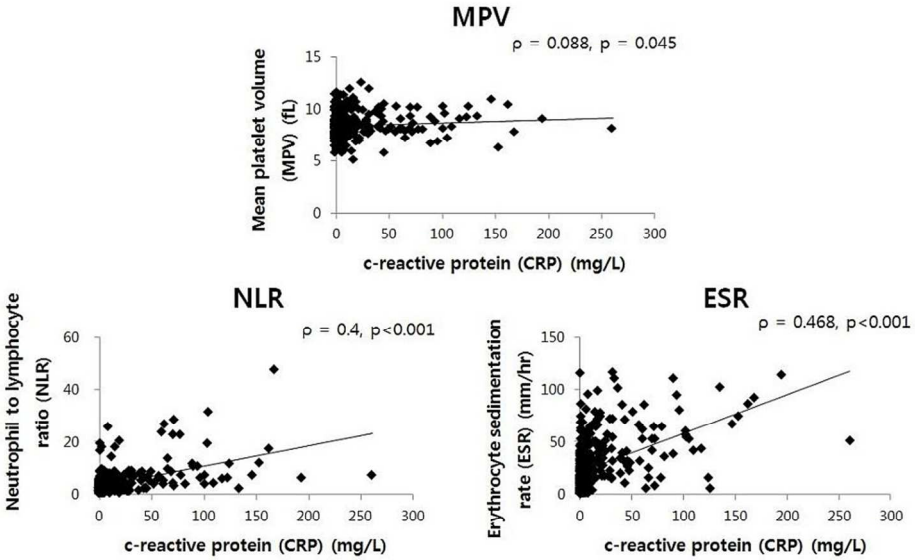

Figure 1. The correlation between mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR), erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) in cerebral infraction patients
Abbreviations: ρ, Spearman's rank correlation coefficient.

90x68mm (300 x 300 DPI)

STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1-2
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	4
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	4-5
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	5
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	N/A
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	5
Test methods	7	The reference standard and its rationale.	N/A
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	5
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	N/A
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	N/A
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	N/A
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	4-5
	13	Methods for calculating test reproducibility, if done.	N/A
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	5
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	5
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	N/A
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	N/A
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	N/A
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A
	20	Any adverse events from performing the index tests or the reference standard.	N/A
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	N/A
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	5-6
	24	Estimates of test reproducibility, if done.	N/A
DISCUSSION	25	Discuss the clinical applicability of the study findings.	6-7

BMJ Open

Characteristics of platelet indices, neutrophil to lymphocyte ratio and erythrocyte sedimentation rate compared with c-reactive protein in cerebral infarction patients: a retrospective analysis of comparing hematologic parameters and c-reactive protein

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Primary Subject Heading:	Haematology (incl blood transfusion)
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Keywords:	IMMUNOLOGY, HAEMATOLOGY, Stroke medicine < INTERNAL MEDICINE

Research article

Characteristics of platelet indices, neutrophil to lymphocyte ratio and erythrocyte sedimentation rate compared with c-reactive protein in cerebral infarction patients: a retrospective analysis of comparing hematologic parameters and c-reactive protein

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Abstract

Objective: Elevation of c-reactive protein (CRP) is one of the major acute-phase response following ischemic or hemorrhagic stroke. This study aims to investigate the associations between platelet indices, neutrophil to lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) compared with CRP in cerebral infarction patients.

Setting: The clinical data of cerebral infarction patients were analyzed retrospectively.

Participants: We analyzed unduplicated 516 cerebral infarction patients (mean age: 66.2±12.7, Male /Female= 291/225).

Outcome measures: Mean platelet volume (MPV), mean platelet volume to platelet count (MPV/PC), NLR and ESR were compared with CRP in cerebral infarction patients in a single institute through Spearman correlation test.

Results: There were significant correlations between CRP and MPV ($\rho = 0.088$, $p = 0.045$), NLR ($r = 0.4$, $p<0.001$), and ESR ($r = 0.468$, $p<0.001$) in cerebral infarction patients. In male group, NLR ($\rho = 0.398$, $p<0.001$) and ESR ($\rho = 0.502$, $p<0.001$) showed significant correlations with CRP. In female group, CRP showed significant correlations with MPV ($\rho = 0.17$, $p = 0.011$), NLR ($\rho = 0.392$, $p<0.001$), and ESR ($\rho = 0.475$, $p<0.001$).

Conclusions: MPV, NLR, and ESR showed significant correlation with CRP in cerebral infarction patients. MPV, NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer. Further well designed and large scale prospective studies are warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

Key words: Mean platelet volume, Mean platelet volume/platelet count, Neutrophil to lymphocyte ratio, Erythrocyte sedimentation rate, Cerebral infarction

Strengths and limitations of this study

- Mean platelet volume (MPV), neutrophil to lymphocyte ratio (NLR) and erythrocyte sedimentation rate (ESR) were positively associated with c-reactive protein (CRP) in cerebral infarction patients, especially female patients.
- MPV, NLR and ESR may be useful parameters for evaluating cerebral infarction patients compared with CRP.
- MPV or NLR are cost effective and simple parameters can be attainable by automatic hematology analyzer.
- Further well designed studies are warranted to understand the exact meaning of platelet indices and NLR in monitoring of cerebral infarction patients

INTRODUCTION

There have been many efforts to find useful diagnostic markers for monitoring cerebral infarction patients. C-reactive protein (CRP) is a marker of inflammation and a hallmark of the acute-phase response.[1] Many reports suggested that CRP was associated with risk of stroke,[2-4] whereas, some report did not find significant relations.[5 6] Recently, Liu et al. reported that higher high sensitivity-CRP (hs-CRP) concentrations were associated with a higher risk of ischemic stroke, particularly for non-fatal stroke, male and hypertensive subjects but there were no significant associations between hs-CRP and intracranial hemorrhage (ICH) and subarachnoid hemorrhage (SAH) in a large prospective study.[7] Also, erythrocyte sedimentation rate (ESR), a classical acute phase marker was often compared with CRP. Recently, there were a number of reports dealt with platelet indices such as mean platelet volume (MPV), and MPV/platelet count (PC) ratio have clinical meanings in various conditions such as atherosclerosis,[8 9] cerebral infarction,[10] or active inflammatory diseases,[11 12] even high MPV was associated with fractures.[13] Also, neutrophil to lymphocyte ratio (NLR) parameter was reported to be an important measure of systemic inflammation.[14] However, the platelet indices or NLR have not been fully investigated to role as a useful surrogate biomarker of diagnosis of cerebral infarction patients. This study aims to show any association between platelet indices, NLR and ESR compared with CRP in cerebral infarction patients.

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Retrospectively, we analyzed unduplicated 516 cerebral infarction patients (mean age:

66.2±12.7 year, male to female ratio: 1.3 (291 to 225)) whose MPV, MPV/PC ratio, NLR and ESR were compared with CRP from January 2010 to September 2013. All patients' medical data were ethically protected and were solitary analyzed for this retrospective study. CRP levels were determined by HiSens hsCRP LTIA (HBI Co., Ltd., Anyang, Korea), latex-enhanced turbidimetric immunoassay, as read on the TBA-200FR NEO automated clinical chemistry analyzer (Toshiba Medical Systems Corporation, Tochigi-ken, Japan). PC, MPV, and NLR were measured by Beckman Coulter LH 750 or 780 (Beckman Coulter, Miami, USA) hematology analyzers. ESR was measured by TEST 1 (Alifax, Padova, Italy), a closed automated analyzer determines the ESR which uses the aggregation capacity of RBCs by telemetry.[15]

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RESULTS

The analyzed parameters were not normally distributed ($p<0.05$), therefore we trusted Spearman correlation analysis. CRP showed significant correlations with MPV ($\rho = 0.088$, $p = 0.045$), NLR ($\rho = 0.4$, $p<0.001$), and ESR ($\rho = 0.468$, $p<0.001$) in cerebral infarction

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DISCUSSION

There were many factors of cerebral infarction pathogenesis. We thought activated platelet could be produced in various cerebral vascular diseases and these conditions might increase

MPV. The inflammation seems to be related with the pathogenesis of cerebral infarction. Inflammation is found to develop at a sufficiently early stage in progressive ischemic brain injury.[16] Besides cerebral infarction, our previous study showed a positive correlation of C-reactive protein (CRP) with MPV/PC, and NLR were noted in pneumonia patients.[17] Recently, there were various studies which dealt with relationship between hematologic indices and cerebral infarction.[18- 20]

Arikanoglu et al. reported that CRP and MPV are higher in the ischemic stroke patients who died in comparison to those who survived.[18] MPV is a novel index for silent cerebral infarction regardless of classical cardiovascular risk factors.[19] Also, NLR predicts poor prognosis in ischemic cerebrovascular disease.[20] Although, CRP level and outcome of ischemic stroke is under debated,[21] the inflammation might be related with of certain progression of cerebral infarction. Therefore, CRP is one of representative inflammatory marker, it seems to be useful to compare new parameters with CRP in cerebral infarction patients.

For the first time, this study showed MPV and NLR as expected ESR could be statistically correlated with CRP in moderate number of cerebral infarction patients. We identified MPV was correlated with CRP in overall and female group, but was not correlated in male group. A report suggested that women had a higher median platelet count than men in Korea.[22] A few studies suggested that men had slightly higher MPV than women.[23] [24] Only female MPV showed significant correlation with CRP. The exact causes of gender difference were not uncovered but it might be caused from a difference of platelet count or hormone differences between women and men. In Pearson correlation analysis, CRP showed significant correlations with MPV/PC ($r = 0.164$, $p<0.001$), NLR ($r = 0.517$, $p<0.001$), and ESR ($r =$

0.479, p<0.001) in cerebral infarction patients. However, all analyzed parameters were not normally distributed, we considered it is proper to interpret data by Spearman correlation test. Both NLR and ESR were positively correlated with CRP in Pearson or Spearman correlation tests.

This study might support further related studies dealt with an association between cerebral infarction and inflammation. Also, MPV, NLR and ESR should be further investigated to have a clinical impact of disease progression and expectation of mortality in cerebral infarction patients. Up to date, the consensus diagnostic cut-off ranges of MPV and NLR has not been established for evaluation of cerebral infarction. Furthermore, platelet indices measures the femto-liter (10^{-15} L) levels and still has not been standardized and it showed the result variations within device to device.[25] This study has some limitations such as we retrospectively analyzed patients group for quite a long time (3 years and 8 months). We did not categorize specific cerebral infarction types and did not strictly exclude patients with additional disease such as diabetes, cardiovascular diseases, malignant diseases might impact level of enrolled parameters. In addition, MPV can be influenced by the time interval between sampling and analysis.[26] MPV results become increasingly unreliable after 4 hours.[27] Complete blood count (CBC) analysis in our laboratory has been almost proceeded within 2 hours from sampling start.

In conclusion, we newly suggested a possibility of MPV and NLR may be useful parameters for evaluating cerebral infarction patients compared with CRP. Characteristically, MPV or NLR are inexpensive and simple parameters can be attainable by automatic hematology analyzer. Therefore, further well designed and large scale prospective studies are warranted to evaluate platelet indices or NLR for monitoring cerebral infarction patients.

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Contributors

Jong-Han Lee designed and participated in all stages of the study. Kyum-Yil Kwon consulted diagnosis of patients. Soo Young Yoon, Hyon-Suk Kim and Chae Seung Lim helped to consultations of this study.

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Competing interests

None declared.

Provenance and peer review

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Data sharing statement

No additional data are available.

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Arikanoglu et al. reported that CRP and MPV are higher in the ischemic stroke patients who died in comparison to those who survived.[18] MPV is a novel index for silent cerebral infarction regardless of classical cardiovascular risk factors.[19] Also, NLR predicts poor prognosis in ischemic cerebrovascular disease.[20] Although, CRP level and outcome of ischemic stroke is under debated,[21] the inflammation might be related with of certain progression of cerebral infarction. Therefore, CRP is one of representative inflammatory marker, it seems to be useful to compare new parameters with CRP in cerebral infarction patients.

For the first time, this study showed MPV and NLR as expected ESR could be statistically correlated with CRP in moderate number of cerebral infarction patients. We identified MPV was correlated with CRP in overall and female group, but was not correlated in male group. A report suggested that women had a higher median platelet count than men in Korea.[22] A few studies suggested that men had slightly higher MPV than women.[23] [24] Only female MPV showed significant correlation with CRP. The exact causes of gender difference were not uncovered but it might be caused from a difference of platelet count or hormone differences between women and men. In Pearson correlation analysis, CRP showed significant

correlations with MPV/PC (r = 0.164, p<0.001), NLR (r = 0.517, p<0.001), and ESR (r = 0.479, p<0.001) in cerebral infarction patients. However, all analyzed parameters were not normally distributed, we considered it is proper to interpret data by Spearman correlation test. Both NLR and ESR were positively correlated with CRP in Pearson or Spearman correlation tests.

This study might support further related studies dealt with an association between cerebral infarction and inflammation. Also, MPV, NLR and ESR should be further investigated to have a clinical impact of disease progression and expectation of mortality in cerebral infarction patients. Up to date, the consensus diagnostic cut-off ranges of MPV and NLR has not been established for evaluation of cerebral infarction. Furthermore, platelet indices measures the femto-liter (10^{-15} L) levels and still has not been standardized and it showed the result variations within device to device.[25] This study has some limitations such as we retrospectively analyzed patients group for quite a long time (3 years and 8 months). We did not categorize specific cerebral infarction types and did not strictly exclude patients with additional disease such as diabetes, cardiovascular diseases, malignant diseases might impact level of enrolled parameters. In addition, MPV can be influenced by the time interval between sampling and analysis.[26] MPV results become increasingly unreliable after 4 hours.[27] Complete blood count (CBC) analysis in our laboratory has been almost proceeded within 2 hours from sampling start.

In conclusion, we newly suggested a possibility of MPV and NLR may be useful parameters for evaluating cerebral infarction patients compared with CRP. Characteristically, MPV or NLR are inexpensive and simple parameters can be attainable by automatic hematology analyzer. Therefore, further well designed and large scale prospective studies are warranted to

evaluate platelet indices or NLR for monitoring cerebral infarction patients.

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Jong-Han Lee designed and participated in all stages of the study. Kyum-Yil Kwon consulted diagnosis of patients. Soo Young Yoon, Hyon-Suk Kim and Chae Seung Lim helped to consultations of this study.

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Competing interests

None declared.

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Data sharing statement

No additional data are available.

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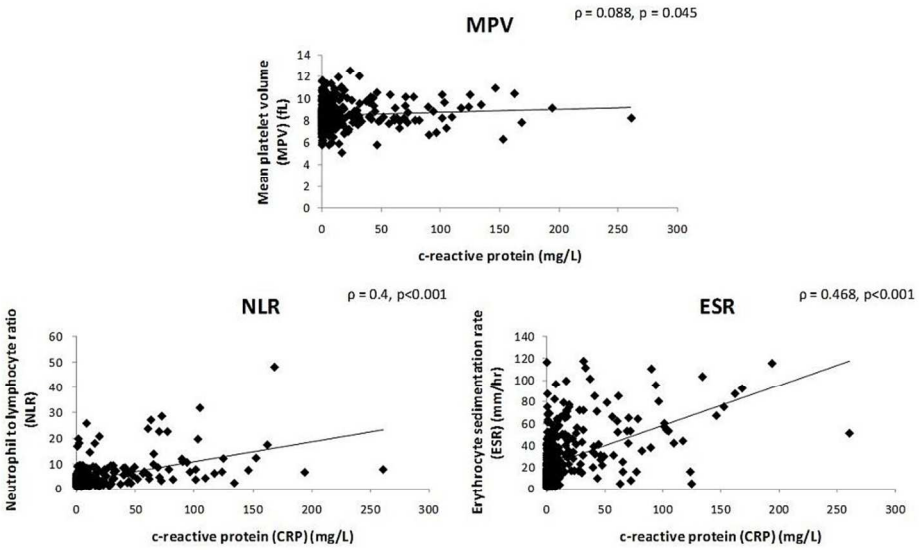

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STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1-2
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	4
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	4-5
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	5
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	N/A
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	5
Test methods	7	The reference standard and its rationale.	N/A
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	5
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	N/A
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	N/A
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	N/A
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	4-5
	13	Methods for calculating test reproducibility, if done.	N/A
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	5
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	5
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	N/A
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	N/A
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	N/A
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A
	20	Any adverse events from performing the index tests or the reference standard.	N/A
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	N/A
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	5-6
	24	Estimates of test reproducibility, if done.	N/A
DISCUSSION	25	Discuss the clinical applicability of the study findings.	6-7