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Original Article

The Value of Perfusion Index in Predicting the Prognosis of Multiple Trauma Patients

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Abstract

Aim: To determine the value of peripheral perfusion index (PI) in predicting the prognosis and concurrent organ injuries in multiple trauma (MT) patients.

Materials and Methods: A prospective observational study of 50 patients with MT and 50 healthy volunteers presenting to the emergency department (ED) was conducted. PI measurements were made during the initial evaluation of the patient. PI 1% and below were grouped as low and above 1% as high.

Results: There was statistical significance between the groups in terms of gender, ISS score averages, PI and SI values, and both SBP and IBP (p=0.007, 0.011, <0.001, <0.001, respectively). When the trauma region and admission PI values are compared, there is statistical significance in terms of the presence of pneumothorax, spleen injury, emergent intra-abdominal operation and mortality (p=0.004 and 0.006, respectively). The median spleen injury stage was 2 in the group with high PI while the median stage 4 spleen injury was found in the group with low PI. There is statistical significance between PI values according to survival percentages for the first 24 h, 7 and 30 days (p=0.006). PI was significantly lower in exitus group.

Conclusion: PI was found to be a promising tool to predict the presence of shock, mortality and organ spesific injuries in MT patients early at admission.

Keywords: Perfusion index, emergency department, multi-trauma, hemorrhagic shock

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INTRODUCTION

Multipl trauma (MT) is defined as significant traumas involving more than one major organ system or one organ system and at least two large bones (1). MT severity is determined by the existing life-threatening injuries which one of those is hemorrhagic shock, a clinical condition that occurs with blood loss and compromises tissue perfusion and oxygenation (2).

Tissue oxygenation is possible when the oxygen demand required to maintain the aerobic metabolism to the tissues and the amount of oxygen presented to the tissues are in balance (3). Critically ill patients cannot respond appropriately to ischemic stimuli due to endothelial and arteriolar smooth muscle damage and therefore, global hemodynamic parameters [such as blood pressure (BP), heart rate (HR)] may not adequately reflect peripheral blood flow (4,5).

The perfusion index (PI) is used to evaluate the pulsatile power in the selected region. It expresses the pulsatile signal coming from the arterial as a percentage of the non-pulsatile signal and is measured with a pulse co-oximeter using infrared (640-940 nm) rays (6). It is a bedside tool and recorded numerically. The measuring device is reusable and portable in small sizes. The PI provides instantaneous and continuous feedback on the perfusion status of the selected monitoring area (7). Changes in PI provide information about regional vasoconstriction (decrease in PI) and vasodilation (increase in PI) (8).

Many markers, including clinical, regional and global, are used to evaluate tissue perfusion, but simple, applicable, objective data and scores suitable for use in emergency services are needed. Thus, in our study, the prognostic utility of PI in MT patients was investigated.

MATERIALS AND METHODS

This study was conducted prospectively and observationally in the emergency department (ED) of a tertiary care trauma hospital between 10.05.2017-30.05.2018. Ethical approval was obtained from the Instutional Review Board. Appropriate patient consent form has been obtained from all the patients. In the form, the patient has given oneself consent for his/her images, and other clinical information to be reported in the journal. The patient understands that name and initials will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

A total of 100 patients, 50 of whom were healthy and 50 patients who were admitted to the ED, over the age of 18, brought with MT were included in the study. Injury severity score (ISS) was used for MT assessment. Patients with ISS ≥15 were considered as MT. Patients who were brought to the ED as cardiopulmonary arrest, were referred to our hospital after the first intervention from an external center, had ISS <15, were younger than 18 years of age and did not accept to participate in the study were not included in the study. Three of 56 patients who were thought to be clinically MT were excluded from the study because they did not meet the definitions of MT, 2 had their first intervention performed in an external center, and 1 person did not want to participate in the study. The remaining 50 MT cases with 50 volunteers without a history of trauma were included in the study as the control group for comparisons. Informed consent form was obtained from the patient oneself if he/she was conscious, or from their first-degree relatives if they are conscious but unstable or had altered consciousness. Demographic data, vital signs [BP, HR, fever, arterial oxygen saturation (SaO_2)], shoch index (SI), PI measurement values, detailed radiological image comments of injured systems were recorded in the patient study form. On the 7th and 28th days; clinical outcome, operations, if any, in which service the patient was admitted, hospital records were examined; In the absence of hospital records, they were called by phone and added to the study form.

Radical-7® Pulse CO-Oximeter® is a noninvasive monitor that measures SaO_2, HR and PI with optional (with a disposable removable additional probe) hemoglobin (Hb), carboxyhemoglobin (COHb), total oxygen content (TOC), methemoglobin (MetHb), pleth variability index, acoustic respiratory rate (RR) and pleth RR. The device rainbow technology uses 7+ wavelengths of light to continuously and non-invasively measure COHb, MetHb, and total Hb and provide more reliable closed probe detection. The TOC provides a calculated measure of the amount of oxygen present in arterial blood, which can provide useful information on both oxygen dissolved in plasma and oxygen combined with Hb. RR can be determined via acoustic or plethysmographic waveform. It can take the form of a detachable, portable handheld device for carrying the patient (7). According to the recommendations of the manufacturer, if the PI is 1% or less, the perfusion of the measured region is low, and if it is above 1, the perfusion is normal.

The research data were uploaded to the computer environment and evaluated with the SPSS 20 (Statistical Package for Social Sciences) program. Since at least one of the comparative groups was under 30 cases in descriptive statistics, non-parametric tests were used and descriptive statistics were expressed as median (min-max), categorical variables as n (%). The significance of the difference between the two groups in categorical variables was calculated using the "Chi-Square Test", and the comparison of the median values of the continuous variables in the two groups was calculated using the Mann-Whitney-U test. ROC curve was used as a statistical method for performance criterion calculations. Statistical significance level was accepted as $p<0.05$.

RESULTS

There was a statistically significant difference between the groups in terms of demographic data and clinical characteristics with regards to gender, systolic blood pressure (SBP), SaO_2, PI and SI values (Table 1). According to the PI values of the patients; the mean ISS scores, SI, both SBP and diastolic blood pressure (DBP) were statistically significant ($p=0.007$, 0.001, <0.001 and <0.001, respectively) (Table 2).

Table 1. Demographic characteristics of the patient and control groups

	Group		
	Patient	**Control**	**p***
	Median (min-max) / n (%)		
Age (years)	36 (18-91)	32 (19-56)	0.302
Gender			0.009?
Female	6 (12%)	17 (34%)	
Male	44 (88%)	33 (66%)	
Trauma type			-
Fall down	8 (16%)	-	
Pedestrian injury	17 (34%)	-	
Passenger injury	16 (32%)	-	
Motorcycle	2 (4%%)	-	
Penetrating injury	7 (14%)	-	
SBP (mmHg)	123 (64-190)	125 (85-168)	0.225
≤90 mmHg	6 (12%)	1 (2%)	0.050?
>90 mmHg	44 (88%)	49 (98%)	
DBP (mmHg)	72 (30-110)	80 (60-105)	0.003
HR (beats/min)	90 (60-142)	80 (52-117)	0.003
SI	0.76 (0.34-2)	0.62 (0.45-1.06)	0.003
Normal	24 (48%)	36 (72%)	0.023?
Mild	13 (26%)	10 (20%)	
High	13 (26%)	4 (8%)	
Fever (°C)	36 (0-37)	36 (36-367)	0.007
SaO2 (%)	95 (83-99)	97 (94-100)	<0.001?
Low	17 (34.7%)	-	
Normal	32 (65.3%)	50 (100%)	
PI(%)	1.7 (0.1-7)	3.8 (0.5-13)	0.002?
Low (<%1)	13 (26%)	2 (4%)	
Normal (≥%1)	37 (74%)	48 (96%)	

*Mann-Whitney-U test, ?Chi-square test SBP, Systolic blood pressure; DBP, diatolic blood pressure; HR, heart rate; SI, shock index; SaO_2, arterial oxygen saturation; PI, perfusion index

Table 2. Correlation of age and clinical parameters in low and normal PI groups

	PI(%)		
	Low (<%1)	Normal (≥%1)	p*
	Median (min-max) / n (%)		
Age (years)	33 (19-78)	35 (18-91)	0.969
Gender			1.000
Female	3 (20%)	20 (23.5%)	
Male	12 (80%)	65 (76.4%)	
SBP (mmHg)	110 (70-159)	126 (64-190)	0.007
DBP (mmHg)	67 (35-93)	78 (30-110)	0.032
HR (beats/min)	100 (70-142)	83 (52-117)	<0.001
SI	0.97 (0.44-2)	0.65 (0.34-1.57)	<0.001
Fever (˚C)	36 (35-36.7)	36 (26-367)	0.212
SaO2 (%)	96 (83-100)	97 (85-100)	0.518
ISS	41 (17-75)	25 (17-48)	0.007
Intensive care unit	6 (46.1%)	9 (24.3%)	0.170?
Death	4 (30.7%)	-	0.003?

*Mann-Whitney-U test, ?Chi-square test PI, perfusion index; SBP, Systolic blood pressure; DBP, diatolic blood pressure; HR, heart rate; SI, shock index; SaO2, arterial oxygen saturation; ISS, injury severity Score

Table 3. Comparision of patient groups according to concurrent organ damages and PI

	Present (n)	Absent (n)	PI<1	P>1	p
Head trauma	29	21	8	21	0.764
Spinal trauma	18	32	5	13	0.830
Chest trauma	36	14			0.239
Pneumothorax	15	35	8	7	0.004
Hemothorax	14	36	5	9	
Contusion	14	36	4	10	
Abdominal trauma	20	30			0.895
Spleen injury	10	40	4	6	
Kidney injury	5	45	0	5	
Hepatik injury	7	43	1	6	
Retroperitoneal haemorrhage	2	18			
Intraabdominal haemorrhage	17	3			
Hollow organ injury	1	19			
Emergent surgery	8	41	5	3	0.006
Extremity injury	33	17	8	25	0.693

Table 4. Comparison of mortality and perfusion index

PI (n=50)	Alive n (%)	Exitus 0th day	7th day	28th day	p
Low PI	9 (69.2)	3 (23.1)	1 (7.7)	0 (0.0)	p=0.006
High PI	36 (97.3)	0 (0.0)	0 (0.0)	1 (2.7)	
Total	45 (90.0)	3 (6.0)	1 (2.0)	1 (2.0)	

Low PI: ≤1, High PI: >1

Table 5. Comparison of demographic and clinical parameters between clinical outcomes

	Death	Alive	p*
	Median (min-max) / n(%)		
Age	30 (24-35)	38 (18-91)	0.210
Gender			1.000
Female	-	6 (13%)	
Male	4 (100%)	40 (86.9%)	
Trauma type			
Fall down	1 (25%)	7 (15.2%)	
Pedestrian injury	2 (50%)	15 (32.6%)	
Passenger injury	-	16 (34.7%)	
Motorcycle	-	2 (4.3%)	
Penetrating injury	1 (25%)	6 (13%)	
PI	0.51 (0.10-0.80)	2.00 (0.42-7.00)	0.002
Low (<%1)	4 (100%)	9 (19.5%)	0.003
Normal (≥%1)	-	37 (80.4%)	
SBP (mmHg)	75 (70-83)	128.5 (64-190)	0.002
≤90 mmHg	4 (100%)	2 (4.3%)	<0.001
>90 mmHg	-	44 (95.6%)	
DBP (mmHg)	45 (35-67)	75 (30-110)	0.010
HR (beats/min)	133.5 (100-142)	88 (60-116)	0.003
SI	1.65 (1.42-2)	0.7 (0.34-1.57)	0.001
Normal	-	24 (52.1%)	0.002
Mild	-	13 (28.2%)	
High	4 (100%)	9 (19.5%)	
Fever (˚C)	36 (35-36)	36 (26-36.8)	0.100
SaO2 (%)	90 (83-94)	95.5 (85-99)	0.053
Low	2 (66.6%)	15 (32.6%)	
Normal	1 (33.3%)	31 (67.3%)	
Lactate (mmol/L)	5.2 (5.2-5.2)	2.2 (1.5-8.9)	0.124
0-2	-	9 (36%)	0.080
2.1-3.9	-	13 (52%)	
>4	1 (100%)	3 (12%)	

*Mann Whitney-U test P, perfusion index; SBP, Systolic blood pressure; DBP, diatolic blood pressure; HR, heart rate; SI, shock index; SaO2, arterial oxygen saturation; ISS, injury severity Score

When the patients included in the study were evaluated in terms of the trauma region, the presence of pneumothorax and advanced stage spleen injury were statistically significant in the low PI group (Table 3). The median spleen injury stage was 2 in the group with high PI spleen injury, and the median stage 4 spleen injury was found in the group with low PI. A statistically significant difference was found between the PI groups in terms of spleen injury stage medians ($p<0.05$). The existing organ injuries of the patients and their relationship with PI are given in Table 3.

From a prognostic point of view, there is statistical significance between PI values in terms of emergency intra-abdominal surgery and mortality (Tables 3 and 4). Splenectomy was performed in 5, liver segmentectomy in 2, and diaphragmatic rupture repair in 1 of the patients who were taken to the emergency operation. Of the MT patients included in the study, 1 died in ED, 2 died in the

emergency operation, 1 died in the first 7 days (day 2), and 1 died in the first 30 days (26th day). For the remaining of 45 patients, no mortality was observed in the first 30 days. Demographic and clinical comparison of PI values is given in Table 5.

DISCUSSION

Monitoring of macrohaemodynamic and microcirculatory parameters, which has recently drawn considerable scientific interest in critical care, has also been increasingly popular in ED (9). It has been shown by a number studies that patients with acute circulatory failure are negatively affected by longstanding macrohaemodynamic and/or microcirculatory changes (10,11). As far as we know, PI on MT patients has been studied by only one observational study, and our study is the second of its kind but we have important differences and remarkable study results.

Herein, we primarily sought to study PI's predictive role in MT patients. The main finding of our study is that PI was a strong predictor of death in patients with MT (Table 4, 5). The second outcome is prediction of concurrent organ injuries and our study demonstrates that advanced spleen injury and pnx are statistical significant findings in patients whom Pİ values are <1. Beside these it can be a good predictor of emergent abdominal surgery as a result of trauma (Table 3). It has been reported that death early after MT (by 24 hours) most commonly occurs secondary to the injury to the central nervous system, which is followed by hypovolemia secondary to bleeding into or out of the body. When no other cause exists, hypotension is the major sign of bleeding. However, hypotension occurs late during hypoperfusion, only after a patient has lost almost a third of circulating blood volume (12-15). From a technical standpoint, BP provides circulatory force, and PI is derived from a photoelectric plethysmographic signal obtained by a pulse oximeter. Therefore, PI may provide real-time data on peripheral blood flow and BP, with circulation being impaired when BP is reduced (10). As BP decreases, pulsatile blood flow to the periphery decreases. With the results we obtained in our study, supported by the theory, we can say that low PI indicates low blood pressure. In addition, when 90 mmHg was accepted as the threshold, a statistically significant difference was found between the PI groups for SBP below 90 (Table 2). PI can be used as a performance measure for the significant difference between PI values and hypotension. This was reflected by a significant drop in SBP and DBP in the low-PI group in our study. Thus, we hypothesize that PI may be an early sign of death and haemorrhage in MT patients. It is therefore highly plausible that serious and/or longstanding circulatory fluctuations coupled with increased sympathetic tone would be mirrored by PI levels or their variability (9). Also observation of statistical significances between PI groups and SBP, SI, ISS score (Table 2), suggests that the injury may be more severe in patients with MT who had a lower admission PI and PI can be a good prognostic factor. Since addressing life-threatening injuries is the priority of the evaluation of MT (15), PI values and all of the three variables can be used in conjuction to assess MT patients. However, to our opinion, this task may wast valuable time in these patients. This notion was corroborated by the fact that patients with a low PI had a significantly higher SI and an ISS >15.

The study was conducted as a pilot study. The single center and small number of patients are the biggest limitations of the study. It is therefore not possible to generalize. The control group was selected from the working people. In order to confirm the data obtained, randomized controlled multicenter studies with a larger number of patients are required.

CONCLUSION

PI was found to be a useful parameter to predict the presence of shock, spesific organ injuries (pneumothorax and spleen) and mortality in patients with MT. It is a quick and easy method that can also be used to determine the severity in the initial evaluation of the patient during the triage stage in the ED. Predicting advanced stage injury of an organ with high hemorrhagic potential, such as the spleen, suggests that it has the potential to be useful with vital signs and parameters of shock staging, but needs to be supported by future studies.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The ethical approval of this study was taken from Univercity of Health Sciences, Ankara Numune Training and Research Hospital (E-17-1407).

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Original Article

The Possibilities of Nurses (Health Care Service Providers) Making Medical Errors

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Abstract

Aim: The aim of this study was to determine the medical error probabilities of the healthcare provider nurses.

Materials and Methods: The study is descriptive and cross-sectional and the sample consisted of 235 nurses. Participant information form and the malpractice tendency scale were used to collect the data. SPSS 21 package program was used in the analysis of the data and ethical principles were adhered to at every stage of the research.

Results: 195 (83%) of the participants are women, 57 (24.3%) of them work in intensive care. 180 (76.6%) nurse graduates, 199 (84.7%) people are subject to 657. The level of satisfaction in the profession was the lowest 35 (14.9%) and the highest was 39 (16.6%). It was found that the medical error tendencies of the female participants were lower than the men, and a significant difference was found when gender and drug and transfusion applications, falls, communication and scale total scores were compared ($p<0.05$). A statistical significance was determined when age and drug and transfusion applications, falls, and scale total score were compared ($p<0.05$). It was found that there was a significant difference between the weekly working time and the dimensions of falls and nosocomial infections ($p<0.05$). When the falls dimension, hospital infections dimension, patient follow-up / material safety dimension, communication dimension and scale total score were compared, a significant difference was found ($p<0.05$).

Conclusion: Medical error tendency is an issue that needs to be carefully considered for the nurses who are most in contact with the patient. Considering the total score obtained from the scale, it can be said that nurses' tendency to make medical mistakes is quite low. It can be said that especially the level of satisfaction in the profession affects almost all sub-dimensions and the entire scale.

Keywords: Malpractice, health, medical error, nurse

CITATION

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INTRODUCTION

Hospitals are among the most complex businesses of our time, so the services offered there must also have a high level of reliability (1). The adjective "safe", which is one of the features in health services, is defined as preventing the services provided from harming the patient rather than benefiting them, causing injury, disability and death, and making mistakes (2).

Medical practice errors, the intervention envisaged or applied by the health care personnel during the delivery of health services, the wrong medical technique used, the patient's illness going beyond the normal course of the patient's illness, a decrease in the quality of life, the occurrence of various types of morbidities and even mortality. may result (3). Medical error is defined as negligence with potentially negative consequences, regardless of whether or not there are any negative consequences from the side of the patient.

According to the Health Institutions Accreditation Joint Commission, medical error; It has been defined as the situation where the patient is harmed due to the ethical and inappropriate behavior of the healthcare professional who provides health services, and the negligent and inadequate behavior in professional practices (4). “Incorrect medical practice according to the Rules of Professional Ethics of Medicine; It is defined as a patient's harm and malpractice of medicine due to insufficient knowledge, inexperience or indifference (5). Professional responsibility in the ethical principles and responsibilities section for nurses published by the Turkish Nurses Association (2009); It is stated that it is related to the prevention of possible damages and to take responsibility for the implementation (6).

Medical practice errors are caused by environmental factors, medical equipment and technical factors as well as human factors (7). Faulty medical practices are usually seen as a result of carelessness, negligence, professional inexperience, and non-compliance with relevant orders and regulations. medical errors; surgical errors, medication errors, errors in diagnosis, errors due to system failure, errors due to negligence, work-related errors and application-related errors (8-10).

Mistakes that occur during the delivery of health services cause millions of people to suffer and serious economic damage every year around the world (11). As a result of these mistakes, which mostly occur due to inexperience, ignorance, indifference and the technologies being used, situations such as injury, disability, death or delayed treatment occur (12). The study conducted in Turkey by Çakmak, Konca and Teleş (2018) "Turkish National Security Reporting System (GRS) to detect medical errors, covered the medical error cases that occurred between 23/03/2016 and 31/12/2017 . In the most reported error types; laboratory errors came first and surgical errors came second (13).

There is no legal regulation that requires special sanctions on health personnel for malpractice claims in Turkey. Nurses, who constitute a significant majority among all health workers; They encounter the risk of medical error more frequently than other types of occupations due to reasons such as the excess, diversity and continuous continuity of their dependent and independent functions (14). By identifying medical errors and the causes of errors made by healthcare professionals, it can ensure that these errors are intervened, prevented and corrected before they reach the patient (15).

Determining the areas where healthcare providers make medical mistakes and the most common mistakes, and the presence of a law on medical error will also reduce the possibility of medical errors and medical errors of individuals.

MATERIALS AND METHODS

Type of Research: The research is descriptive and cross-sectional.

Place of Research: The research was conducted in a city hospital.

The Universe/Sample of the Study: The population of the research consists of nurses working in a city hospital. No method was chosen as the sampling method, and it was aimed to reach the entire universe. The research was completed with 235 healthcare professionals (73% of the population) due to reasons such as the participants being on annual/maternity leave, filling in the questionnaires incompletely and not wanting to participate in the research.

Data Collection Tools: In the research, "Participant Information Form" and "Malpractice Tendency Scale" were used.

Participant Information Form: The structured participant information form used in data collection was developed by the researchers in line with the literature. in form; demographic information such as gender, marital status, age, education level, unit of employment, total working time in the profession, title, staff status, and questions about medical error. This form consists of 71 questions.

Malpractice Tendency Scale (Medical Error Tendency Scale in Nursing): The scale developed by Özata and Altunkan (2010) was created to evaluate nurses' tendency to make medical errors. The scale consists of 5 sub-dimensions and a total of 49 questions. Its sub-dimensions are drug and transfusion applications, falls (5 items), hospital infections (12 items), patient monitoring/material safety (9 items), and communication (5 items) consisting of 18 items. The scale is a 5-point Likert type and is scored between 1 and 5. The relationship between the mean score of the scale and making medical mistakes is inverse. In other words, as the average score increases, it shows that the probability of nurses to make medical errors is low. While the maximum score that can be obtained from the scale is 245, the minimum is 49 points. The Cronbach alpha coefficient of the scale was found to be 0.95 (Özata & Altunkan, 2010). In this study, the Cronbach's alpha coefficient of the scale was found to be 0.87.

Application of Data Collection Tools: The data of the research were obtained from the health professionals working in a city hospital (only nurses were included), informing them about the research and obtaining their verbal consent to participate in the research; The data were collected by participants answering the questions online (whatsapp).

Statistical Analysis

Data analysis was performed with the Statistical Package for the Social Sciences (SPSS) 23.0 package program. In the study, Kolmogorov Smirnov test was applied to conform to normal distribution. Parametric test techniques were used in the study due to the normal distribution of the data. In the evaluation of parametric (continuous) variables; arithmetic mean, standard deviation, minimum and maximum values were used, and frequency and percentage were used in the evaluation of nonparametric (discontinuous) variables. In the analysis of data between groups, t-test/chi-square/ and ANOVA tests were used in independent groups.

RESULTS

Demographic characteristics of the participants are given in Table 1. 195 (83%) of the participants were female and 40 (17%) were male. 57 (24.3%) of the nurses work in the intensive care unit and 11 (4.7%) in the delivery room. 180 (76.6%) nurses have a bachelor's degree, 170 (72.3%) nurses are married and 158 (67.2%) nurses have children. 199 (84.7%) people subject to 657 and only 20 (8.5%) people are responsible nurses. The majority of the participants (n=111) worked in the profession for 1-5 years and 121 (51.5%) of the nurses were mixed-workers. Considering the level of satisfaction in the profession, the majority (n=82) are nurses saying "3", 39 (16.6%) saying "1" and 35 (14.9%) saying "5".

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In Table 2, the scores of the participants in the malpractice scale and its sub-dimensions are given. There are 18 items in the dimension of drug and transfusion practices, 5 items in the dimension of falls, 12 items in the dimension of hospital infections, 9 items in the dimension of patient follow-up and 5

Table 1. Demographic Characteristics of the Participants

		n (235)	%
Gender	Woman	195	83.0
	Male	40	17.0
Working Unit	Internal service	38	16.2
	Surgical Service	42	17.9
	Operating room	15	6.4
	Intensive care	57	24.3
	Emergency	22	9.4
	Delivery room	11	4.7
	Other services	50	21.3
Education Status	Health vocational high School	19	8.1
	Associate Degree	28	11.9
	Licence	180	76.6
	Degree	8	3.4
Marital status	Single	65	27.7
	Married	170	72.3
Child Presence	Yes	158	67.2
	No	77	32.8
Squad Status	subject to 657	199	84.7
	4-B	36	15.3
Title	Nurse-Midwife	215	91.5
	Responsible Nurse	20	8.5
Total Working Time in Occupation	Less than 1 year	4	1.7
	1-5 years	111	47.2
	11-15 years	42	17.9
	16-20 years	26	11.1
	More than 21 years	52	22.1
Your Working Time in This Department	Less than 1 year	60	25.5
	1-5 years	115	48.9
	6-10 years	40	17.0
	11-15 years	14	6.0
	16-20 years	2	0.9
	More than 21 years	4	1.7
The shift you usually work	Daytime	68	28.9
	Night	46	19.6
	Day and night	121	51.5
Level of Satisfaction in the Profession	1	39	16.6
	2	27	11.5
	3	82	34.9
	4	52	22.1
	5	35	14.9
	Mean±SS		
Age	34.53±8.171		
Weekly Working Time	52.89±49.595		
Number of Watches per Month	8.67±19.626		
Number of Patients Given Daily Care	47.29±129.701		

items in the dimension of communication. The highest score that can be obtained from each dimension is 5.00. Considering the scale scores, it can be said that the tendency of nurses to make medical mistakes is low.

Table 2. Scores of the Participants from the Malpractice Scale and its Sub-Dimensions

	n	Mean±SS	Min.	Max
Drug and Transfusion Applications	235	4.71±.70	1	5
Falls	235	4.38±.87	1	5
Hospital Infections	235	4.61±.78	1	5
Patient Monitoring/Material Safety	235	4.46±.81	1	5
Communication	235	4.62±.78	1	5

Table 3 shows the comparison of the characteristics of the participants and the scale scores used. It is seen that female participants' medical error tendencies are lower than males. A significant difference was found when gender was compared with drug and transfusion applications, falls, communication and scale total score ($p<0.05$). Statistical significance was determined when age, drug and transfusion applications, falls and scale total score were compared ($p<0.05$). It was determined that there was a significant difference between the weekly working time and the dimensions of falls and hospital infections ($p<0.05$). Considering the total working time in the profession; Although it was observed that those who worked less than 1 year had almost no tendency to medical errors, there was no significant difference between the lengths of work and dimensions both in the profession and in the service ($p>0.05$). Those with the highest level of satisfaction in their profession had the highest propensity to medical error (4.83±.666), that is, lower tendency to medical errors, and those with the lowest satisfaction level had the lowest score (4.45±.995), that is, medical errors. error propensity was found to be higher. A significant difference was found when the dimensions of falls, nosocomial infections, patient monitoring/material safety dimension, communication dimension and scale total score and satisfaction level were compared ($p<0.05$). It can be said that as the level of satisfaction increases, the probability of medical error decreases.

Table 3. Comparison of Participants' Characteristics and Scale Scores Used

	n=235	D.T.P		Falls		H.E.		P.M/M.S		Communication	
Gender	Woman	4.77	.539	4.45	.760	4.65	.665	4.49	.749	4.68	.680
	Male	**4.37**	**1.181**	4.06	1.251	4.43	1.204	4.31	1.096	4.35	1.127
Test and p	t	3.355		2.575		1.593		1.213		2.497	
	p	.001		.011		.113		.226		.013	
Age		4.71	.703	4.38	.872	4.61	.784	4.46	.818	4.62	.782
Test and p	F	.672		2.032		1.990		1.156		1.388	
	p	.908		.002		.003		.273		.094	
Total Working Time in Occupation	Less than 1 year	5.00	.000	4.50	1.000	4.98	.042	5.00	.000	4.95	.100
	1-5 year	4.62	.799	4.22	.958	4.52	.869	4.30	.869	4.58	.795
	11-15 year	4.71	.708	4.37	.952	4.48	.957	4.40	1.007	4.42	1.068
	16-20 year	4.85	.269	4.51	.618	4.77	.411	4.64	.561	4.80	.460
	More than 21 year	4.80	.639	4.66	.624	4.80	.530	4.69	.567	4.76	.581
Test and p	F	1.081		2.108		2.001		2.119		1.729	
	p	.367		.054		.095		.052		.144	
Your Working Time in This Department	**Less than 1 year**	4.69	.699	4.38	.812	4.63	.721	4.47	.835	4.60	.857
	1-5 year	4.71	.694	4.34	.936	4.55	.865	4.35	.880	4.70	.659
	11-15 year	4.59	.875	4.33	.916	4.64	.764	4.56	.735	4.84	.431
	16-20 year	4.91	.135	4.66	.511	4.79	.513	4.79	.366	5.00	.000
	More than 21 year	4.97	.039	5.00	.000	5.00	.000	4.89	.157	4.80	.400
		4.98	.032	4.80	.283	4.98	.042	4.86	.167		
Test and p	F	.587		.745		.585		1.272		.569	
	p	.710		.591		.711		.277		.724	
Level of Satisfaction in the Profession	1	4.45	.995	3.94	1.252	4.24	1.276	3.99	1.176	4.22	1.252
	2	4.66	.614	4.08	.818	4.49	.665	4.26	.781	4.52	.853
	3	4.75	.635	4.51	.736	4.72	.595	4.53	.706	4.75	.483
	4	4.77	.581	4.46	.759	4.64	.686	4.56	.689	4.65	.716
	5	4.83	.666	4.68	.616	4.82	.533	4.79	.523	4.82	.546
Test and p	F	1.817		5.231		3.501		5.795		3.999	
	p	.126		.000		.008		.000		.004	

*D.T.P: Drug and Transfusion Practices, H.E: Hospital Infections, P.M/M.S.: Patient Monitoring/Material Safety, t: Independent Samples t test, F: One Way ANOVA test

DISCUSSION

In the study conducted with 235 nurses, when the scores of the participants from the scale were examined, it was seen that the tendency of the nurses to make medical errors was quite low. In the study they conducted with nurses in surgical clinics, Dgın and Özkan (2020) determined that nurses had a positive attitude towards medical error (16). Gök and Sarı (2017) stated in their study with nurses working in the pediatric service that nurses showed a positive attitude towards medical error (17). In the study conducted by Ulusoy and Tosun (2020) to determine the medical error attitudes of physicians and nurses, it was observed that the medical error attitudes of the participants were generally positive, and the awareness of the importance of medical error and error reporting was high (18). In a study conducted by Cebeci et al. with 203 nurses, they determined the tendency of nurses to medical errors (19). As a result of the study, it was determined that the probability of nurses to make medical errors is low. In the study conducted by İntepeler et al. with nurses, the tendency to medical error was found to be low. Our study overlaps with and supports other studies in the field of medical error tendency (20).

The demographic characteristics of the participants and the scores they got from the scale were discussed in the light of the literature. Female participants were found to be less prone to medical errors than males in all dimensions. When drug and transfusion applications, falls, communication and scale total scores were compared between men and women, a significant difference was found. In the studies of Öztürk and Özata (2013), it was observed that the tendency to make mistakes is higher in female nurses (21). In our study, it is seen that the scale score decreases periodically as the working time increases. This may be due to reasons such as shift work, fatigue and stress over the years. In the study of Er and Altuntaş, nurses mostly; it has been determined that factors such as inexperience, fatigue, heavy workload, long working hours, and professional inexperience cause medical errors (22). İntepeler et al. (2014) with 263 nurses, no statistically significant difference was found between the mean medical error tendency scores of nurses according to years of service (20). In a study conducted by Özata and Altunkan (2010), the main reasons for making mistakes in healthcare workers are; workload is high, the number of working nurses is not high, nurses are given work outside of their duties, stress and fatigue (23). In the study of Mayo and Duncan, it was determined that the reason for the occurrence of medical errors was high workload and low level of job satisfaction (24). Işık et al. (2012) emphasized in his study that the reason for medical errors is the lack of communication with doctors, nurses and the busy and tense work environment. According to the nurses, the presence of sufficient personnel, work stress and workload, taking care of more patients due to insufficient nurses, burnout caused by the strict attitude of superiors, and trying to provide care to the patient above their potential in a short time are among the most important causes of medical errors (25).

LIMITATIONS

The research only includes nurses working in a city hospital. The fact that it is single-centered and only nurses are selected as health care providers is a limitation.

CONCLUSION

In the study, it is seen that the medical error tendencies of the nurses are at a very low level. In addition, although nurses' medical error tendencies are low, factors such as fatigue, high workload, and stress can increase the error tendency. In order to eliminate or minimize possible medical errors, policies should be implemented in institutions, routine trainings should be planned, working environments and hours should be regulated.

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Original Article

Correlation of C-Reactive Protein/ Lymphocyte Ratio with Mortality in Patients Diagnosed with COVID-19 in the Emergency Department

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Abstract

Aim: Studies have shown that CRP/lymphocyte ratio (CLR) is a better predictor of prognosis compared to the use of CRP or lymphocyte count alone. The aim of this study is to reveal the relationship of CLR with early mortality in patients hospitalized for COVID-19.

Materials and Methods: The study is a retrospective observational study. Patients aged 18 years and over, who admitted to the emergency department between March 11, 2020 and December 31, 2020, whose PCR test results were positive, and whose treatment was decided to be inpatient, were included in the study. The time interval for mortality is 28 days. The data recorded in the study form were analyzed with the IBM SPSS 20.0 statistical program.

Results: In addition to CRP, lymphocyte and CLR values, troponin, ferritin, and d-dimer values, which have been shown to have prognostic significance in current studies, were found to be statistically significantly different between the groups with and without mortality ($p<0.001$ for all values). Although the AUC value of CLR was 0.834, higher than CRP (AUC=0.808) and lymphocyte (AUC=0.696), the Delong test showed that the difference in the areas under the curve of CLR and CRP values was not statistically significant ($p=0.163$). Considering the power of other parameters to predict mortality, there was no significant difference between CRP, CLR and D dimer AUC values, while troponin AUC value was significantly higher than all other parameters, and ferritin AUC value was significantly lower than all other parameters.

Conclusion: This study showed that the CLR value has a high prognostic value in terms of mortality in COVID-19 patients. While the prognostic power of CLR is significantly higher compared to the lymphocyte count alone, although it provides a numerical superiority compared to CRP, this difference is not statistically significant.

Keywords: COVID-19, lymphocyte, CRP, CRP/lymphocyte ratio, CLR

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INTRODUCTION

C-reactive protein (CRP), an acute phase protein synthesized by hepatocytes, is one of the most frequently used markers to reflect the body's systemic inflammatory response (1). Some studies have shown that changes in CRP levels are associated with prognosis in patients with sepsis (2). There is also an inflammatory process in COVID-19 disease. Studies have shown that CRP is associated with poor prognosis in moderate and severe COVID-19 cases. A parameter that can show the cytotoxic immune response function in COVID-19 patients is the lymphocyte count. Many studies have shown that low lymphocyte count in COVID-19 cases is associated with disease severity, ARDS development, and poor prognosis (3).

CRP indicates systemic inflammatory response and lymphocyte indicates immunological response. Studies in cancer patients have shown that CRP/lymphocyte ratio (CLR) is a better indicator in determining prognosis compared to the use of CRP or lymphocyte count alone (1,4). However, as far as we know, there is no study on the role of CLR value in determining early mortality in COVID-19. In this study, our primary aim is to

reveal the relationship of CLR with early mortality in patients hospitalized in the emergency room with the diagnosis of COVID-19. As a secondary endpoint, the power of CLR value to predict the need for intensive care admission and the correlation of CLR with values such as troponin, ferritin, and d-dimer, which are currently considered valuable in predicting prognosis in COVID-19 patients, were determined.

MATERIALS AND METHODS

The study is a retrospective observational study. The study was initiated following the approval of the ethics committee, and patients aged 18 years and older who applied to the emergency department of a tertiary education and research hospital between 11 March 2020 and 31 December 2020, whose SARS-COV2 PCR test results were positive, and whose treatment was decided to be inpatient, were included in the study. Demographic data of patients, complaints on admission, comorbid diseases, hospitalization times, vital signs, physical examination findings, laboratory results, consultations, disease-related complications if developed (bacterial infection, renal failure, cardiac failure or acute coronary syndrome, shock, ARDS), hospitalization Duration and hospital outcome were obtained from the hospital automation system and patient files by retrospective scanning and recorded in the study forms.

The time interval for mortality is 28 days. Patients hospitalized for more than 28 days were excluded from the study. In addition, patients with negative PCR test results followed up with a preliminary diagnosis of COVID-19 and patients with missing data were also excluded from the study.

Statistical Analysis

Data were made using the IBM SPSS 20.0 (Chicago, IL, USA) statistical program. Whether the distribution of discrete and continuous numerical variables is suitable for normal distribution was investigated by Kolmogorov Smirnov test. Descriptive statistics are shown as mean±standard deviation (SD) or median (minimum - maximum) for discrete and continuous numerical variables, and as number of cases and (%) for categorical variables. Categorical variables were evaluated with Chi-square and continuous variables were evaluated with Mann Whitney U test. The areas under the curve were compared with the Delong test. Results for $p<0.05$ were considered statistically significant.

RESULTS

A total of 895 patient records were reviewed within the study, of which 46% (n=416) were female and the median age was 63 (IQR25-75: 52-73). The most common complaints were cough, fever, and shortness of breath, respectively; Anosmia, which was frequently emphasized in the first period of the COVID-19 epidemic, was observed in only 33% of the patients. The most common comorbid diseases were hypertension, diabetes, and coronary artery disease. Data on the demographic characteristics of the patients are summarized in Table 1.

Table 1. Characteristics of patients

N=895	
Age	63 (IQR 52-73)
Gender	
Female	412 (46%)
Male	483 (54%)
Complaint at admission	
Cough	683 (76.3%)
Fever	579 (64.7%)
Dyspnea	516 (57.7%)
Myalgia	484 (54.1%)
Anosmia	295 (33%)
Diarrhea	196 (21.9%)
Throat ache	146 (16.3%)
Nasal discharge	55 (6.1%)
Comorbid diseases	
Hypertension	456 (50.9%)
Diabetes	331 (37%)
Coroner artery disease	264 (29.5%)
Asthma-COPD	134 (15%)
Chronic kidney disease	100 (11.2%)
Congestive heart failure	92 (10.3%)
Stroke	44 (4.9%)
Others	248 (27.7)

All values given as median (IQR 25-75) or number and percentiles
Abbreviations: IQR: interquartile range, COPD: chronic obstructive pulmonary disease

Of the evaluated patients, 787 were hospitalized to releated service, and 108 were admitted to the intensive care unit. Cytokine storm developed in 95 of the hospitalized patients and 6 of them died. Cytokine storm developed in 107 of the patients admitted to the intensive care unit, and 64 of them died (Figure 1).

Although the gender distribution of the patients admitted to the intensive care unit and the service was similar, the median age value was significantly higher in the patients hospitalized in the intensive care unit ($p<0.001$). The median length of stay was 8 (IQR 25-75: 5-11) days for patients admitted to the ward, and 18 (IQR 25-75: 11-26) days for patients admitted to the intensive care unit. When vital parameters were examined, statistically significantly higher fever, increased pulse and respiratory rate, low saturation and blood pressure were found in patients hospitalized in the intensive care unit. Laboratory parameters of the patients, especially CRP, lymphocyte counts and CLR values, were also compared between the patient groups admitted to the service and intensive care unit. Significant differences were found between the groups in many parameters such as troponin, d-dimer, white blood cell count, and lactate. The vital signs and laboratory parameters of the patients are given in Table 2.

Table 2. Vitals and laboratory parameters of the inpatient and intensive care unit admitted patients

	Patients admitted to inpatient clinic (n=787)	Patients admitted to intensive care unit (n=108)	P value
Gender			0.073
Female	371	41	
Male	416	67	
Age	62 (IQR 51-72)	69.5 (IQR 59-49.75)	<0.001
Vitals			
Fever	37° (IQR 37-38)	38° (IQR 38-38)	
SO2	92 (IQR 89-94)	81 (IQR 78-85)	<0.001
Breath/min	13 (IQR 12-14)	16 (IQR 15-18)	<0.001
Pulse/min	91 (IQR 82-96)	110 (IQR 95-115)	<0.001
Systolic BP mmHg	138 (IQR 125-150)	130 (IQR 110-154)	<0.001
Diastolic BP mmHg	70 (IQR 62-80)	65 (IQR 55-82)	0.006
Laboratory findings			0.015
Glucose(mg/dL)	125 (IQR 106-169)	154 (IQR 122-204.75)	
Creatinine(mg/dL)	0.98 (IQR 0.83-1.14)	1.06 (IQR 0.75-1.69)	<0.001
Albumin(g/L)	3.5 (IQR 3.2-3.7)	2.5 (IQR 2.22-3)	0.06
ALT(IU/L)	27 (IQR 17-47)	29 (IQR 18.25-55.75)	<0.001
AST(IU/L)	32 (IQR 23-49)	40.5 (IQR 26.25-65.75)	0.072
LDH(IU/L)	301 (IQR 245-375)	418 (IQR 344.25-518.25)	0.001
Na(mmol/L)	137 (IQR 134-139)	138 (IAR 135-142)	<0.001
K(mmol/L)	4.19 (IQR 3.9-4.53)	4.25 (IQR 3.83-4.79)	0.004
CRP(mg/L)	**68 (IQR 24-118)**	**127 (IQR 69.75-262)**	**0.52**
WBC(x10^3/µL)	6.4 (IQR 4.9-8.4)	10.6 (IQR 7.02-15.7)	<0.001
Lymphocyte(x10^3/µL)	**1.16 (IQR 0.82-1.57)**	**0.78 (IQR 0.50-1.27)**	**<0.001**
Neutrophile(x10^3/µL)	4.73 (IQR 3.39-6.48)	9.37 (IQR 5.68-14.03)	<0.001
Hemoglobin(g/dL)	13.5 (IQR 12.5-14.6)	11.15 (IQR 9.62-13.1)	<0.001
Platelet(x10^3/µL)	210 (IQR 166-279)	205 (IQR 152-284.25)	<0.001
MPV(fL)	9.7 (IQR 9-10.3)	10.2 (IQR 9.6-11.10)	0.316
Ferritin(µg/L)	285 (IQR 146-541)	544.5 (IQR 281.5-1161)	<0.001
Troponin(ng/L)	5 (IQR 3-11.6)	39.5 (IQR 11.18-77)	<0.001
D-dimer(ng/mL)	660 (IQR 410-1190)	2335 (IQR 1220-4240)	<0.001
pH	7.4 (IQR 7.38-7.43)	7.4 (IQR 7.34-7.46)	<0.001
PCO^2(mmHg)	38.4 (IQR 35.7-41.1)	38.95 (IQR 33.75-43.37)	0.20
HCO^3(mEq/L)	24.7 (IQR 23.5-26.1)	23.55 (IQR 20.3-27.17)	0.58
Lactate(mmol/L)	1.45 (IQR 1.2-1.75)	1.91 (IQR 1.46-2.29)	0.007
CLR	57.3 (IQR 19.89-117.85)	143.3 (IQR 74.2-338.48)	<0.001

All values given as median (IQR 25-75) or numbers
Abbreviations: IQR: interquartile range, n: number, SO2: oxygen saturation, min: minute, BP: blood pressure, ALT: alanine amino transferase, AST: aspartate amino transferase, LDH: lactate dehydrogenase, Na: sodium, K: potassium, CRP: C reactive protein, WBC: white blood cells, MPV: mean platelet volume, PCO^2: partial carbon dioxide pressure, HCO^3: bicarbonate, CLR: C reactive protein / lymphocyte ratio

As the primary endpoint of our study, CRP, lymphocyte and CLR values used to predict mortality, as well as troponin, ferritin and d-dimer values, which were shown to have prognostic significance in current studies, were statistically significantly different between the groups with and without a mortal course ($p<0.001$ for all values). (Table 3). The area under the curve (AUC) was calculated by performing ROC analysis for all values. Although the AUC value of CLR was 0.834, higher than CRP (AUC=0.808) and lymphocyte (AUC=0.696), the Delong test showed that the difference in the areas under the curve of CLR and CRP values was not statistically significant ($p=0.163$). In the analyzes performed for CLR to predict mortality, the sensitivity was calculated as 80%, specificity 76%, positive predictive value (PPV) 22% and negative predictive value (NPV) 97.8% for the120-cutoff value. For the same purpose, the sensitivity for the CRP 100 value is 80%, the specificity is 66%, the PPV is 16.7%, and the NPV is 97.5%. (Table 3, Figure 2)

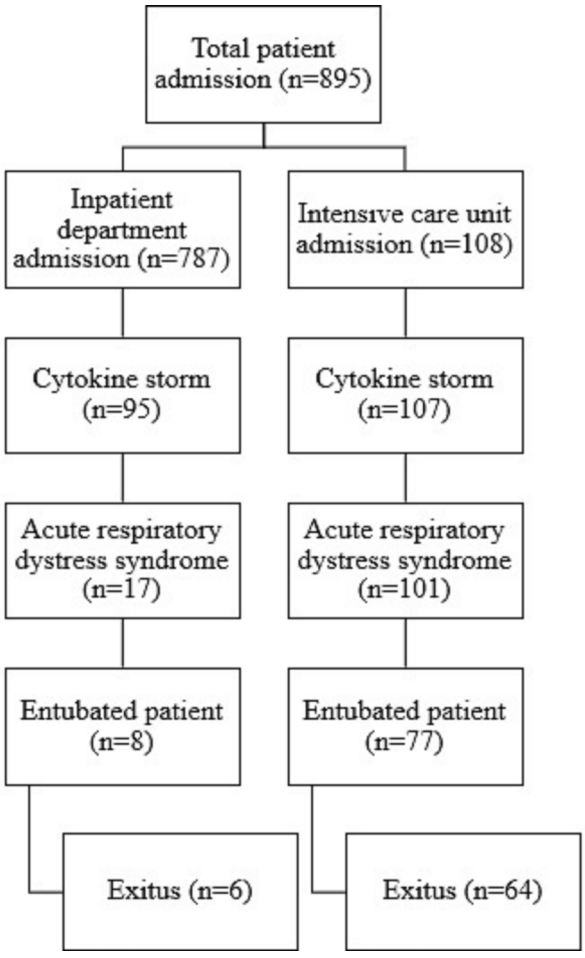

Figure 1. Flow chart

When the power of other parameters such as troponin, D dimer and ferritin to predict mortality was examined, the highest AUC value was found for troponin (0.905) and the lowest for ferritin (0.706). While there was no significant difference between the AUC values of CRP, CLR and D dimer with the Delong test performed, the AUC value of troponin was significantly higher than all other parameters, and the AUC value of ferritin was significantly lower than all other parameters (Delong test, $p<0.05$). (Figure 2)

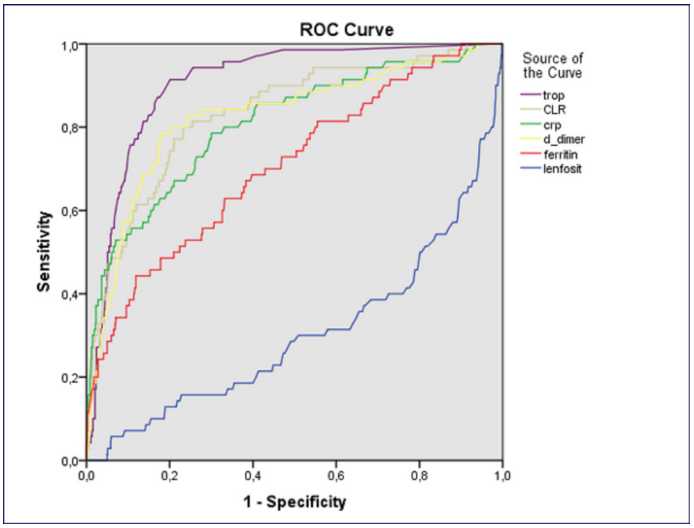

Figure 2. ROC curve of parameters to predict mortality

The predictive power of CLR value in determining the development of cytokine storm, development of ARDS and need for intensive care hospitalization, which are important endpoints in clinical practice apart from mortality, was evaluated by ROC analysis, but the area under the curve was not found as high as for mortality (Figure 3).

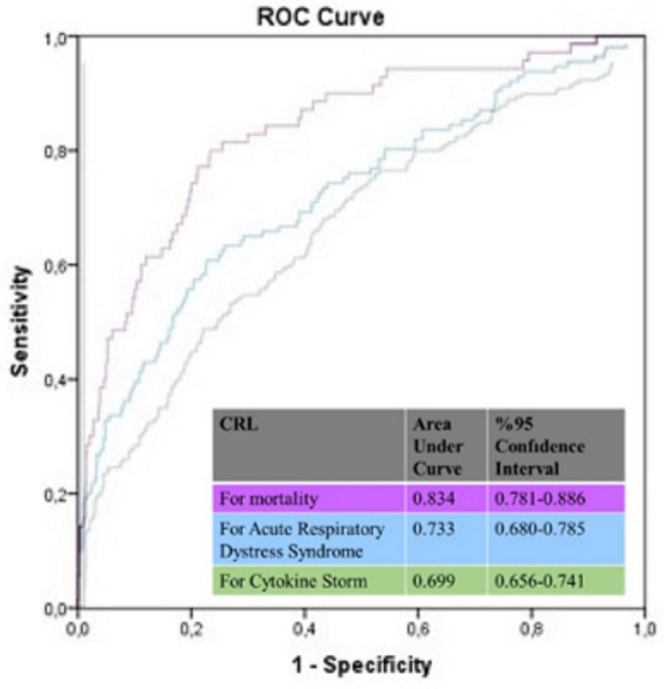

Figure 3. ROC curves of CRL for different clinical outcomes

Table 3. Prognostic value of laboratory parameters for prediction of mortality

	Sensitivity %	Specificity %	PPV %	NPV %	Cutoff level	AUC	%95 CI
CLR	80	76	22	97	120	0.834	0.781-0.886
CRP	80	66	17	98	100	0.808	0.750-0.867
Lymphocyte*						0.696	0.623-0.770
D dimer	83	76	22	98	1250	0.825	0.768-0.883
Troponin	91	80	28	99	15	0.905	0.874-0.937
Ferritin	67	61	12	95	400	0.706	0.639-0.773

Abbreviations: PPV: positive predictive value, NPV: negative predictive value, AUC: area under curve, CI: confidence interval, CLR: C reactive protein/ lymphocyte ratio, CRP: C reactive protein
*Because of the negative correlation between lymphocyte number and mortality (1-AUC) level was give at the table

DISCUSSION

We have two important results in this study, in which we investigated the prognostic importance of CLR value in patients hospitalized in the emergency department due to COVID-19. First, although CLR value is a good predictor of mortality, it does not provide a significant advantage when compared to the use of CRP alone, but it is a stronger prognostic marker than lymphocyte count alone. Our second result is that, when compared with other prognostic markers, CLR is better under the curve in predicting mortality than ferritin, worse than troponin, and has similar strength to d-dimer.

Although COVID-19 pneumonia seems to be losing its effect today, it caused a sudden and excessive increase in the burden of the health system for a while. Exceeding the service capacity has made it necessary to prioritize patients, pushing physicians to search for parameters that help predict patients who may have a bad course. Many markers such as troponin, D-dimer, ferritin, CRP have been used as prognostic markers. In terms of ease of access in hematological parameters, these are the markers that have been researched in this context (3).

Studies have shown that apoptosis-induced lymphopenia develops in conditions such as sepsis, burns, major surgery or trauma, and this condition is associated with a poor prognosis (5). Similarly, Mendez et al. demonstrated the relationship between the presence of lymphopenia and clinical severity and mortality in patients with community-acquired pneumonia (6). The literature shows that approximately two-thirds of COVID-19 patients develop lymphopenia, and this has been associated with a poor prognosis in most studies (7). In our study, the lymphocyte count was significantly lower in patients requiring intensive care admission than in patients requiring ward admission. However, when the predictive power of lymphocyte count in terms of mortality is considered, the AUC value is sufficient to be accepted as a marker, but it is not as high as other markers.

The lymphocyte count is not the only value affected in the hematopoietic system in COVID-19 patients; neutrophilia, thrombocytopenia, and hypercoagulation are also observed, and these variables were found to be associated with poor prognosis (8). Yang et al. tried to find a better marker by combining these variables in one parameter with calculations such as neutrophil /lymphocyte ratio, lymphocyte /monocyte ratio, platelet / lymphocyte ratio; described the neutrophil / lymphocyte ratio as an independent marker for poor clinical outcome (9).

CRP is an acute phase reactant that rapidly rises in the inflammatory response (10). In studies similar to lymphocyte, CRP was found to be high in two-thirds of the patients, and this situation was found to be associated with a poor prognosis (7). Liu et al. used the neutrophil / lymphocyte ratio and CRP values in combination with the logistic regression model they prepared, and they revealed that the predictive power in terms of prognosis with this use is higher than when these variables are used alone (11).

A meta-analysis with COVID-19 patients similarly argued that CLR is an important indicator for poor prognosis (12). In our study, it was shown that high CLR value was associated with poor prognosis, in line with the literature. This prognostic difference was significantly higher than the lymphocyte counts alone. However, when compared to CRP, although CLR showed a numerical superiority in terms of prognosis, this difference was not statistically significant.

Apart from hematological parameters and CRP, many parameters such as liver and kidney function tests, myocardial enzymes, inflammatory markers, glucose, and sodium levels have been investigated prognostically in patients with COVID-19 (13). Studies support the idea that it is not sufficient to evaluate a marker alone, and that it would be appropriate to consider different variables together. Although troponin stood out with its high AUC value among the markers studied in our study, the AUC values of CRP, CLR and D-dimer were found to be similar.

Limitations

The limitations of this study are that the study was conducted in a single center, the data of outpatients were not included in the

analysis, and the criterion determined in terms of prognosis was only 28-day mortality.

CONCLUSION

In this study, in which we examined the prognostic value of the CLR value, which we obtained by dividing the CRP value by the lymphocyte number, in COVID-19 patients, when the AUC value was examined in terms of mortality, it was shown that CLR has a high prognostic power. While the prognostic power of CLR is significantly higher compared to the lymphocyte count alone, although it provides a numerical superiority compared to CRP, this difference is not statistically significant.

Competing interests: The authors declare that they have no competing interest.

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Ethical approval: The ethical approval of this study was taken from Ankara Keçiören Research and Training Hospital

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Case Report

Traumatic Rotatory Atlantoaxial Subluxation

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Abstract

Trauma is one of the most important causes of mortality and morbidity in Turkey as well as in the world. The NCHS data (2021) revealed that trauma was the most common cause of death after heart disease, cancer, and COVID-19 in the USA. Many anatomical regions can be affected due to trauma. Although it constitutes only 3.7% of all trauma patients, the type of trauma with higher mortality and morbidity than other trauma types is cervical spine trauma. In this study, we presented a 20-year-old female patient who brought to the emergency department by her relatives due to a complaint of neck pain after a traffic accident. The patient's history revealed that the traffic accident was low-energy trauma and in-vehicle. It also acknowledged that the patient did not receive direct trauma to her neck, but she had hyperflexion-hyperextension movements of the neck region. Midline cervical spine examination revealed tenderness, but no focal neurological examination findings. Pathological findings were not detected in the cervical plain radiography. Cervical spinal CT (Figure 2) and cervical MRI (Figure 3) imaging were performed on the patient whose symptoms continued. The atlantoaxial dislocation was detected in the imaging of the patient. Although radiography is normal, advanced imaging methods should be used in the presence of positive physical examination findings.

Keywords: Cervical trauma, rotatory atlantoaxial dislocation, cervical tomography, cervical Mr

CITATION

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INTRODUCTION

Trauma is one of the most important causes of mortality and morbidity in Turkey as well as in the world (1). The NCHS data (2021) revealed that trauma was the most common cause of death after heart disease, cancer, and COVID-19 in the USA (2). However, among these causes, deaths due to trauma are the most preventable causes (3).

Many anatomical regions can be affected due to trauma. Although it constitutes only 3.7% of all trauma patients, the type of trauma with higher mortality and morbidity than other trauma types is cervical spine trauma (4). In the case of cervical trauma, a spinal injury may be in the form of subluxation-dislocation or fracture with/without damaging the spinal column (5). While plain radiography is used first in the diagnosis of cervical pathologies, computed tomography (CT) and magnetic resonance imaging (MRI) methods are used in case of further examination (6,7).

In this study, a case that applied to the emergency department with the complaint of neck pain after cervical spine trauma is presented. Cervical plain radiography was normal. The patient underwent CT and MRI due to positive findings in the physical examination and diagnosed with rotatory atlantoaxial dislocation.

CASE REPORT

A 20-year-old female patient was brought to the emergency department by her relatives due to a complaint of neck pain after a traffic accident. The patient's history revealed that the traffic accident was low-energy trauma and in-vehicle. It also acknowledged that the patient did not receive direct trauma to her neck, but she had hyperflexion-hyperextension movements of the neck region.

Blood pressure was 110/60 mmHg, heart rate was 90/min, oxygen saturation was 95%, body temperature was 36.5°C.

In the physical examination of the patient, her general condition was good. She was conscious, oriented, and cooperative. In her neurological examination, her Glasgow Coma Score (GCS) was 15. Midline cervical spine examination revealed tenderness, but there was not any focal neurological examination findings. After the first evaluation, it was determined that there was tenderness in the cervical region. X-ray was indicated in the patient according to the National Emergency X-Radiography Utilization Study (NEXUS) cervical vertebra criteria. Thereupon, routine laboratory and direct radiography imaging examinations applied to trauma patients. Pathological findings were not detected in the

cervical plain radiography (Figure 1). Cervical spinal CT (Figure 2) and cervical MRI (Figure 3) imaging were performed on the patient whose symptoms continued. The atlantoaxial dislocation was detected in the imaging of the patient. The patient was consulted with the neurosurgery clinic. It was learned that the patient who treated conservatively discharged 4 days later with nonsteroidal anti-inflammatory analgesia, cervical collar, and recommendations. The patient with fully functional neck movements continues to follow-up in the neurosurgery clinic.

Figure 1. Normal Cervical Plain Radiography

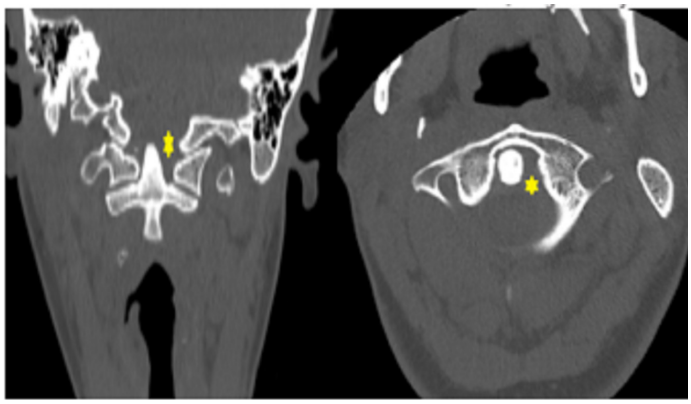

Figure 2. Cervical Spinal CT (atlantoaxial dislocation)

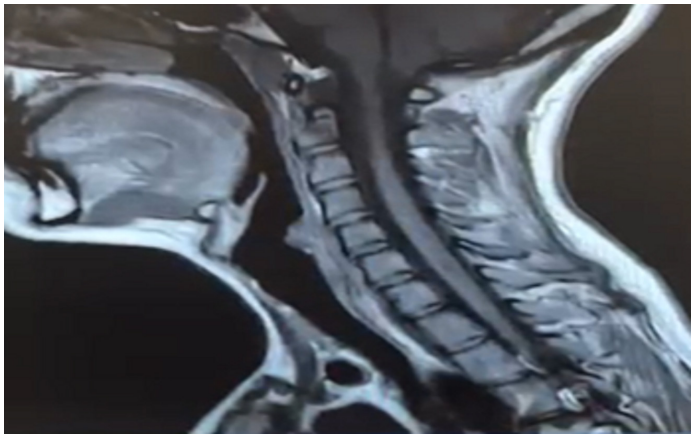

Figure 3. Cervical MRI

DISCUSSION

Trauma is common in Turkey as in the world. Cervical spine trauma is seen in only 3.7% of trauma cases (4). Anamnesis and physical examination are very valuable in patients with cervical spine trauma. The timing of the trauma, the mechanism of the trauma (traffic accident, falling), the movement of the neck during the trauma (hyperextension, hyperflexion, rotational movement), the type of trauma (low/high energy) should be asked during anamnesis. If a patient has any neurological symptoms, when it started and how its course changed should be questioned in detail (8). After taking a detailed anamnesis, a physical examination should be performed. Redness and swelling during cervical spine examination suggest the presence of edema/hematoma. The presence of tenderness, pain, and irregularity in midline palpation of the cervical spine suggests a pathological condition. In addition, muscle strength, sensation, deep tendon reflexes, and the presence of focal neurological signs should be investigated (9).

The need for radiological imaging is decided by using NEXUS Criteria and Canadian C-Spine Rule in patients who admit to the emergency department due to cervical spine trauma (10). Tenderness in the midline of the cervical spine is an important reason for radiological imaging. In patients with suspected cervical injury, radiological evaluation should be performed with radiography, CT, or MRI (4). It has been found that cervical spine injury is missed due to insufficient radiological imaging in 4-30% of cervical traumas (11). Therefore, it is important to choose an appropriate radiological imaging method. In cervical spine imaging, radiography has a sensitivity of 45%, a specificity of 97%. CT has a sensitivity of 99%, a specificity of 100%. MRI has a sensitivity of 97.2%, a specificity of 98.5% (6,7,12).

Since CT is taken in the axial, coronal, and sagittal planes, it causes the cervical structures to be seen more clearly. In addition, CT is faster, and the technical error rate is less than radiography. For these reasons, CT is the preferred method in patients with cervical spine trauma (12). Twenty patients with cervical trauma who applied to the emergency department were examined in a case study. It was reported that CT was superior to plain radiography at a rate of 20% in detecting cervical trauma (13). In another published meta-analysis, CT was found to be significantly more sensitive than plain radiography (14). In a study conducted in the USA, 1583 trauma patients who were admitted to a level 1 trauma center were examined. Cervical spine damage was detected in 4.9% of the patients, and it was reported that CT was superior to X-ray in 64% (15). In another retrospective study, 106 patients with blunt trauma were examined and 4 slice CT, 64 slice CT, and MRI were compared. As a result, although 4-slice CT was found to be 3% unsuccessful to show clinically significant ligament damage, 64-slice CT was reported to be as successful as MRI. Thus, CT was found to be reliable in clinically significant cervical trauma (16).

MRI, which has higher sensitivity than CT, is preferred in the

evaluation of soft tissue damage, hematoma, cervical disc, and neuronal structures in a patient with cervical trauma. (17). MRI is superior to CT and radiography. It provides a 3-dimensional image and soft tissue contrast. It also does not use radiation (18). In a study of 85 people with minor trauma with GCS below 14, MRI was found to be superior to CT in demonstrating intramedullary spinal cord damage. It was reported that MR imaging would be helpful in patients whose neurological examination was inconsistent with their imaging (19). While CT and MRI were found to be equally successful in demonstrating bone pathologies, imaging of edema and ligament damage was found to be more successful than MRI in a retrospective study (20). In a large retrospective study in 2018, 63 patients with blunt trauma with a GCS of 8 and below were examined. It was suggested that MRI should be performed when facet joint dislocation is seen on the CT of patients with cervical trauma. Because MRI was found to be superior to CT in showing edema, epidural hematoma, and ligament damage without fracture (21). In a study conducted in Taiwan, it was stated that MRI is 100% sensitive and 90% specific in detecting atlantoaxial subluxation. Even if the atlantoaxial range is normal, there are indirect findings that can be detected in MRI (peridental effusion, lateral facet arthropathy, abnormal spinolaminar line, and abnormal intramedullary signals). It was reported that the diagnosis of atlantoaxial subluxation was successfully established with MRI (18).

CONCLUSION

A detailed history and physical examination are the most important practices to be performed in cases who apply to the emergency department with a complaint of cervical spine trauma. Radiography is often used as the first imaging tool. Although radiography is normal, advanced imaging methods should be used in the presence of positive physical examination findings.

Competing interests: The authors declare that they have no competing interest.

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Informed Consent: Written consent was obtained from.

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TARGET INTERNATIONAL MEDICINE JOURNAL

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Review Article

Field of Use Hyaluronic Acid and its Derivatives

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Abstract

Hyaluronic acid (HA) is a polysaccharide composed of N-acetylglucosamine and D-glucuronic acid. It is a major component of the extracellular matrix and thus found in many tissues. HA has many effects on the organism (wound healing, cell differentiation, viscoelasticity, embryonic development, anti-aging effect, tissue repair, etc.). The most important factor affecting the biological activity of HA is its molecular weight. Nowadays, it is used in many medical fields such as arthrology, rhinology, oncology, dentistry, ophthalmology, aesthetic medicine, and pneumology including cosmetics. HA can be used with drug molecules in drug delivery systems such as liposomes, micelles, microspheres, and nanoparticles. HA is used in tissue engineering as having the reconstruction and regeneration effect of skin, cartilage, ocular tissues, adipose tissue, and vascular tissues. The moisturizing effect of HA is used in ophthalmology. In addition, HA can be used in the treatment of asthma, chronic sinusitis, chronic obstructive pulmonary disease, and bronchiectasis. With the use of cosmetic products including HA, the moisture retention capacity of the skin increases, its elastic structure is strengthened, and the appearance of wrinkles is removed. Research on the usage areas of HA continues. With these studies, it is aimed to make it more suitable for clinical use.

Keywords: Hyaluronic acid, hyaluronic acid derivatives, hyaluronic acid applications, moisturizing effect, arthrology, cancer treatment

CITATION

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INTRODUCTION

Hyaluronic acid (HA) is a polysaccharide with a glycosaminoglycan structure. It consists of N-acetyl glucosamine and D-glucuronic acid. It is one of the most important components of the extracellular matrix (ECM). It is found in neural, epithelial, connective tissues. (1). It was firstly isolated from the vitreous fluid of the eye (2). The molecular weight of HA is between 2x105-107 Da. Its physicochemical characters depend on the variable molecular weight of HA (3).

HA has many biological effects in the organism, some of which are inflammation, wound healing, cell differentiation, viscoelasticity, embryological development, etc. (4). High molecular weight HA (HMW-HA) relatively plays a role in tissue hydration, provides osmotic balance, and stabilizes the structure of the ECM. The molecular weight of HA affects cell entry and receptor affinity. Low molecular weight HA (LMW-HA) can have a proinflammatory effect or cause tumor progression (4). HA can bind to different receptors, thus causing different biological effects. For example, the HA-CD44 receptor is involved in many physiological processes: (a) inflammation; (b) angiogenesis; (c) wound healing; (d) malignant tumors; (e) ECM structure. CD-168 receptor (Receptor for Hyaluronan-Mediated Motility, RHAMM), which has an important role in cell migration, is located on the cell surface. The receptor complex formed by HA and CD-168 plays an active role in tissue repair and inflammation. The receptor responsible for regulating the clearance of glycosaminoglycans are HARE (Hyaluronan Receptor for Endocytosis) receptors (4).

Recently, the studies have increased using HA in pharmaceutical formulations. Moreover, among the most researched topics are the improvement of the therapeutic effect of HA, elucidating the mechanism of action, synthesizing more advanced derivatives (5).

Nebulized HA can be stored in different parts of the respiratory system depending on its concentration and size. HA has a protective effect on the respiratory system (6). However, acute

or chronic toxic effects were observed in studies using different concentrations of HA (7). Its use with other ingredients (alcohol, perfume oil, propellant, cosmetic colorants, plant extracts) may cause some side effects: wheezing, rhinitis, asthma, and conjunctivitis. Moreover, insoluble particles cause lung damage and chronic toxicity. These side effects occur depending on the particle size, exposure time, and concentration. Inhalation toxicity assessment is made for insoluble particles below 10µm.

Cosmetic products used as aerosols may contain nebulized HA (7). In addition, when topical and cosmetic products containing HA were used, it caused side effects such as itching, erythema, and flaking on the skin. An important issue to be considered in aerosol-designed cosmetic products is the safety assessment (8).

Products including HA are in increasing demand due to their various biological effects. The most important markets for HA are thought to be Europe and Asia (Figure 1) (9).

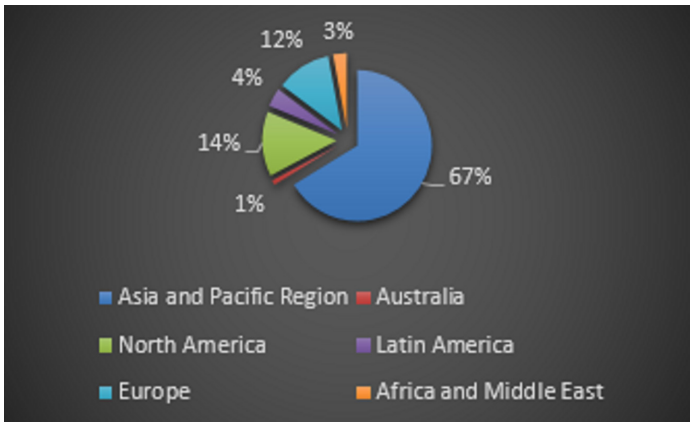

Figure 1. Hyaluronic acid market-regions comparison

Products containing HA and its derivatives were introduced to the cosmetic market a long time ago. In addition, research continues to prove the effectiveness of these products. The reason why HA is used as an active ingredient in cosmetics is that it moisturizes the skin at a good level and has an effect on elasticity. It is also thought to have an anti-wrinkle effect and studies continue in this direction (10).

HA is one of the most commonly used safe and effective ingredients in cosmetic products. Preparations including HA can be used together with different bioactive substances (for example, vitamins, amino acids, plant extracts, proteins, probiotics, minerals, etc.) to increase their effectiveness (11).

Field Of Use Hyaluronic Acid And Its Derivatives

HA is used in many fields in terms of application such as wound therapy, arthrology, soft tissue regeneration, ophthalmology, urology, rhinology, cancer treatment, drug delivery systems, nutrition, and cosmetic due to its biological effects, biocompatibility and safety (Figure 2) (1).

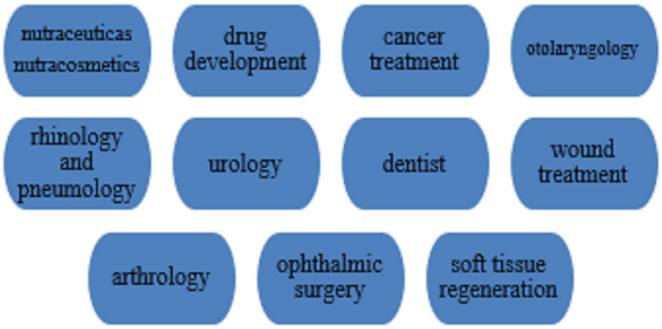

Figure 2. Cosmetic, pharmaceutical and medical applications of HA and its derivatives (12)

HA and its derivatives can be used for ocular, transdermal, cutaneous, oral, and nasal drug targeting. HA can be used with drug molecules in drug delivery systems such as liposomes, micelles, microspheres, and nanoparticles. Drug delivery systems containing HA have enhanced therapeutic effects and physicochemical properties than conventional HA formulations such as solutions. The developed HA formulations can be used in areas such as cancer therapy, controlled drug release, and drug targeting for skin diseases (5,11,13).

Hyaluronic Acid and Cancer

Healthy body cells have a weak HA receptor compared to tumor cells. The reason why HA is expressed more in tumor cells is that tumor cells produce more HA receptors. More production of this receptor presents HA as an alternative in cancer treatment. Docetaxel (DOX) and paclitaxel (PTX) are used in cancer treatment. PTX is a hydrophobic compound and therefore cannot be used for intravenous injection. Conjugation of PTX with HA forms a sufficiently hydrophilic complex and is suitable for injection. To target molecules that are hydrophobic to cancer cells, HA can be loaded into micelles. Polysomes can be used to target both hydrophobic and hydrophilic drugs. The advantage of the PTX-HA conjugate is that it targets CD44 receptors. Liposomes and dendrimers are nanomaterials that may be effective in cancer therapy. HA-coated nanoparticles (NPs), which have an important role in cancer therapy, have increased in importance recently. Another treatment method used in cancer treatment is hyperthermia. HA-based nanoparticles used in this method: gold NPs, NIR loaded NPs, functionalized graphene, oxide NPs, etc. Other uses of HA-based NPs include immunotherapy, photodynamic therapy and sonodynamic therapy (14,15,16).

Effects of Hyaluronic Acid on Tissue

Angiogenesis and inflammation are two important steps in wound healing. Biomaterials containing HA and combined with some biopolymers (hydrogels, sponges and films) were produced and tested. The main advantage of these synthesized biomaterials is increased exudate absorption. Used in tissue engineering, HA is used for the reconstruction and regeneration of skin, cartilage, ocular tissues, adipose tissue, vascular tissues (17,18).

HA is actively used in dentistry because it regenerates hard and soft tissues and provides wound healing in a shorter time. Procedures involving HA used as an adjunct in dentistry: implant osseointegration, papilla reconstruction, stomatitis treatment, and sinus lift (19,20).

Use of Hyaluronic Acid in Ophthalmology

In the orthokeratology treatment used in the treatment of myopia and astigmatism, cornea-shaping lenses are used to correct the refractive defect. The use of HA-containing solutions for the fitting of these lenses was found to be more successful than the saline solution. HA and nisin are linked together using amide bonds. This complex structure has been tested on Gram-positive organisms and has been found to have biocidal capacity. Concomitant use with HA, vancomycin or ciprofloxacin prevented infections in eye surgery. Ophthalmic viscoelastic devices (OVDs) containing HA are used in cataract surgery due to many of their advantages. Long-term use of OVDs can increase intraocular pressure (IOP). A negligible increase in IOP was observed when the two devices were used together. The most common treatment used for dry eye syndrome is the use of artificial tears. Compared to saline solution, artificial tears containing HA have improved visual quality and tear film stability (21,22).

Other Uses of Hyaluronic Acid

HA is used in arthrology, among other things. It offers rheumatoid arthritis, osteoarthritis, and bone cancer patients a promising new therapy option. Osteoarthritis with extensive cartilage damage may benefit from knee joint distraction therapy. Due to the presence of HA in synovial fluid, mesenchymal stromal cells cling to the cartilage (23,24).

The inflammatory condition interstitial cystitis is persistent. Disruption of the bladder mucosa's glycosaminoglycan structure is thought to be the disease's underlying cause (25). A potential therapeutic method is the bladder infusion of chondroitin sulfate (CS) or the combination of CS and HA (26,27).

Vesicoureteral reflux (VUR) in children has been associated with urinary tract infection (UTI) (28). Surgery is the main course of treatment for VUR. However, additional therapies should be taken into consideration because surgical procedures can result in difficulties. Endoscopic injection with polydimethylsiloxane, polyacrylate/alcohol copolymer, dextranomer/HA copolymer, and Teflon is another therapeutic option. There is not much research on the long-term success rate of the Dextranomer/HA copolymer, despite the fact that it has attained a high success rate in a short period of time (29).

Neutrophil elastase levels have been linked to lung-related cystic fibrosis. Because they are anti-inflammatory, polysulfated glycosaminoglycans, which block neutrophil elastases, can be employed in therapy (30). Additionally, HA can be utilized to treat conditions like bronchiectasis, chronic sinusitis, asthma, and COPD (31). The nasal mucosa's post-operative recovery can be aided by the administration of HA in nebule form (32).

The viscoelastic composition, biocompatibility, high hydroscopicity, and non-immunogenicity of HA have made it possible to employ it in cosmetic preparations (33). Aging causes the skin's HA content to diminish. When skin is treated with cosmetics containing HA, its ability to hold moisture rises, its elasticity is enhanced, and wrinkles become less visible (34).

CONCLUSION

In this review, the development and application of hyaluronic acid (HA) and its derivatives in various fields are mentioned. The biological and physiological effects of formulations including HA are explained. Research on the usage areas of HA continues. Studies on possible treatment methods of HA, which is frequently used especially in the field of arthrology, are still continuing. It has been a source of hope in the treatment of diseases such as cancer, cystic fibrosis, interstitial cystitis, and vesicoureteral reflux. HA has a widespread use in the cosmetic field as well as in the medical field. Day by day, it is aimed to gradually expand the usage areas of HA as a result of the studies and to make it more suitable for clinical use.

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