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# Relationship between KRAS and NRAS factors with clinicopathologic findings in patients with metastatic colon cancer

Hamid Saeidi Saedi [1], Fatemeh Nejatifar [2], Kourosh Mojtahedi [3], Moein Moghaddam Ahmadi [3] *

[1] GI Cancer Screening and Prevention Research Center, Department of Radiology, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2] Department of Hematology and Oncology, Razi hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[3] Poursina Clinical Research Development Unit, Guilan University of Medical Science, Rasht, Iran

## Abstract

**Introduction:** Colorectal cancer (CRC) is the third common cancer among human and the fourth common reason of mortalities caused by cancers around the world. During recent years, EGFR-related molecular pathways are known as an important therapeutic pathway. High frequency of mutations of RAS family such as KRAS and NRAS and their rapid incidence in colon cancer indicates their high potential as a biomarker for early detection.

**Materials and Methods:** In this cross sectional retrograde study, patients with colorectal cancer referring to Golestan Razi and Poursina Hospitals in Iran were evaluated during years 2009-2018. The rates of KRAS and NRAS factors were evaluated on paraffinized pathology samples of patients with metastatic colon cancer. Then, the correlation between mutation in these two factors with other clinicopathological findings of patients such as age, gender, tumor grade, location of primary lesion, time to progression (TTP), family history and presence or absence of lymphovascular invasion was investigated.

**Results:** There was no significant correlation observed between occurrence of NRAS and KRAS with age group, family history and gender in the present study. But there was a significant statistical correlation between the rate of NRAS gene incidence with location of primary lesion and tumor grade. Finally, there was found a significant correlation between both KRAS and NRAS genes with TTP, so that TTP of patients reported less than patients without mutations in both groups.

**Conclusion:** The present study showed that presence of both mutations in KRAS and NRAS makes the prognosis of disease worth such a way the location of primary lesion and tumor grade are two effective factors in incidence of NRAS gene and lymphovascular invasion is the effective factor on KRAS gene incidence. also, TTP is lower among patients with mutations in both KRAS and NRAS genes.

**Keywords:** Colorectal cancer, KRAS, NRAS, Mutation

*Corresponding Author: Moein Moghaddam Ahmadi

✉ Email: crdu_poursina@gums.ac.ir

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## Introduction

Colorectal cancer (CRC) is a neoplastic complex and multifactorial disease that as a result of a series of genetic changes, chromosomal abnormalities , mutations ,genetic and epigenetic changes and it has the ability to convert the natural epithelium of the colon to adenocarcinoma (1, 2). CRC is the third most common cancer in the world ,accounting for more than 10% of all new cancers worldwide (3). Approximately, millions of the new colorectal cancer identify around the world every year and nearly half a million people die due to this disease. The risk of colorectal cancer has different changes in the world, as according to studies carried out in the worldwide, the range has been variable between 13 to 66 percent and by comparing to developing areas, it is estimated that the chance of getting infected is more in developed areas (4, 5).

Changes in the cellular genome are affected by the expression or function of genes controlling cell growth and differentiation. Molecular study of cancer helps gene identification that varies in different types of tumors and it helps to explain the role of these genes in carcinogenesis. One of the different genetically changes is receiving the factor of epidermal growth factor receptor (EGFR) that is important in the molecule's target for treating colorectal cancer(6, 7). KRAS (Kirsten rat sarcoma) and NRAS (Neuroblastoma RAS) are the most important downstream molecules of the epidermal growth factor receptor signaling pathway.Three RAS human genes HRAS, KRAS and NRAS are known to be small GTP-GDP binding proteins and act as functional switches by coupling growth receptors to intracellular signaling pathways (6, 8, 9). KRAS and NRAS proto-oncogene encodes a binding protein to a guanosine tri phosphate /guanosine di- phosphate that it is located in intracellular membrane and plays important role in mitogenic transmission signal and cellular response adjustment to the extracellular stimulus such as growth factors ,cytokines and hormones (10, 11).

Researches has shown that mutations in KRAS and NRAS causing loss of GTPase activity from 30 to 50 percent of patients with colorectal cancer (12). High frequency of this mutation and its rapid onset of colon cancer showed the its high potential as a biomarker for the early detection (13). Currently, anti-EGFR antibody has been shown to be an effective therapeutic factor in CRC patients. However, patients with mutations in KRAS and NRAS do not show an appropriate therapeutic response to EGFR antibody. Hence, from the KRAS and NRAS status used as biomarkers to identify patients with mutations (14).

In this study due to increased prevalence CRC and also the impact of the role of gene mutations, especially mutations in RAS genes in the onset of the disease, we decided to investigate the relationship between the KRAS and NRAS factors with the findings of clinicopathologic in patients with the metastatic colon cancer.

## Materials and Methods

In this cross-sectional study retrospectively, patients with colorectal cancer referred to Razi and Poursina hospital Gilan, Iran, during 2009 to 2018 were studied. Inclusion criteria includes all patients with metastatic colon cancer which was confirmed by CT scan or enhanced Carcinoembryonic antigen (CEA).Exclusion criteria also was the lack of willingness of the patient to follow the treatment. Before reviewing patients' cases, all stages of the study were explained and a consent letter were taken from all subjects. In this study, no money was received from patients and the laboratory foundation was responsible for the costs. Accordingly, 67 patients with colorectal cancer were included in the study and the amount of KRAS and NRAS factors were evaluated on a paraffin embedded pathologic specimens of patients with metastatic colon cancer under the supervision of an oncologist by PCR.

The samples from the primary location of the lesion, in case of metastases, was provided from the metastasis location again. Patients in relation to each gene were divided in two categories: 1) Wild type KRAS (no mutation) and none-wild type KRAS (Contains mutation), 2) Wild type NRAS (no mutation) and none-wild type NRAS (Contains mutation). The relationship between the mutations in these two factors with other findings to clinicopathologic patients include age ,sex , grade of tumor ,the lesion of primary ,TTP (Time to progression), family history and existence or non - existence Lymph vascular invasion was analyzed.

**Statistical analyses**

In this study, the collected data were coded and entered into SPSS 22 software. By the use of descriptive statistic, for the qualitative variable (frequency or percentage), normal mean quantitative variable, standard deviation, abnormal median and quadratic range was reported. In inferential experiments, for normal mean quantitative variable T -independent, otherwise nonparametric equivalent Man Whitney were used and for quantitative variable chi square or fisher exact test carried out. Significant level test was $p<0.05$.

## Results

In this study, 67 patients with metastatic colon cancer were investigated. From these 67 samples, in terms of both KRAS and NRAS, 16 cases (23.9%) were not wild-type. Also 10 cases in terms of both KRAS and NRAS were not wild-type either. The average age of individuals in the study were 58.67±10.17 with range of 31 to 78 years of age. According to table 1, a higher percentage of patients (61.2%) were male and also in terms of the location of the primary lesion, more than half of the people (55.2%) rectosigmoid were reported. As results of this study showed that in terms of the tumor grade, more than half of the samples tested (56.7%) high grade were reported. Also, the average of TTP in patients were 10.13±4.58 months, 10 months median, 13 – 7 =IQR and the range of TTP was 2 to 25 months. According to the results, in the terms of family history, 26 of the 67 cases examined (38.8%) were positive and a higher percentage of cases (61.2%) were negative. In terms of lymph vascular invasion also evaluated in patients, 36 cases (53.7%) Lymph vascular invasion was found.

**Table 1.** Demographic and tumor characteristics in patients.

| Variable | | N | % |
|---|---|---|---|
| Age | 30-60 | 33 | 49.3 |
| | >60 | 34 | 50.7 |
| Sex | Male | 41 | 61.2 |
| | Female | 26 | 38.8 |
| Primary lesion location | Ascending colon | 7 | 10.45 |
| | Descending colon | 14 | 20.9 |
| | Transverse colon | 9 | 13.43 |
| | Rectosigmoid | 37 | 55.22 |
| GRID Tumor | low | 13 | 19.4 |
| | intermediate | 16 | 23.88 |
| | high | 38 | 56.72 |
| TTP | Less than 10 months | 40 | 59.7 |
| | More than 10 months | 27 | 40.3 |

In this study, the relationship between the gene expression of NRAS and KRAS with age group, gender, lymph vascular invasion, tumor grade, family history, the location of primary lesion and TTP were analyzed. On the basis of the relationship between gene expression of NRAS and KRAS with age group using Chi -square, no significant correlation was found and it is found that more than half of the patients by age distribution , NRAS and KRAS genes were reported as wild-type (Table 2). There was no significant relationship between NRAS and KRAS gene expression and sex with chi-square test and overall, more than half of the patients (male and female) were wild-type in terms of NRAS and KRAS genes (Table 2).

**Table 2.** Investigation of the relationship between KRAS and NRAS gene expression with demographic.

| Variable | | | NRAS | | | KRAS | | |
|---|---|---|---|---|---|---|---|---|
| | | | None wild | Wild | Total | None wild | Wild | Total |
| Age | 30-60 | N | 11 | 22 | 33 | 7 | 26 | 33 |
| | | % | 33.3 | 66.7 | 100 | 21.2 | 78.8 | 100 |
| | >60 | N | 5 | 29 | 34 | 9 | 25 | 34 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | % | 14.7 | 85.3 | 100 | 26.5 | 73.5 | 100 |
| | total | N | 16 | 51 | 67 | 16 | 51 | 67 |
| | | % | 23.9 | 76.1 | 100 | 23.9 | 76.1 | 100 |
| | **p-value*** | | | 0.074 | | | 0.614 | |
| **Sex** | Male | N | 13 | 28 | 41 | 12 | 29 | 41 |
| | | % | 31.7 | 68.3 | 100 | 29.26 | 70.74 | 100 |
| | Female | N | 3 | 23 | 26 | 4 | 22 | 26 |
| | | % | 11.5 | 88.5 | 100 | 15.4 | 84.6 | 100 |
| | Total | N | 16 | 51 | 67 | 16 | 51 | 67 |
| | | % | 23.9 | 76.1 | 100 | 23.9 | 76.1 | 100 |
| | **p-value*** | | | 0.059 | | | 0.194 | |

The correlation between KRAS gene expression and the primary lesion location with Fisher test was not significant. However, the association between NRAS gene expression and the primary lesion location was significant ($p<0.05$). So that, in 57.1% of patients with primary lesion location in the descending colon, NRAS was mutated and reported as non-wild-type (Table 3). Also according to Table 3, no significant relationship was found between NRAS and KRAS gene expression with family history using chi-square test. The incidence of KRAS gene with a family history was similar to the NRAS results.

**Table 3.** The relationship between KRAS and NRAS gene expression with Primary lesion location and Family history.

| | | | NRAS | | | KRAS | | |
|---|---|---|---|---|---|---|---|---|
| | | | **None wild** | **Wild** | **Total** | **None wild** | **Wild** | **Total** |
| **Primary lesion location** | Ascending colon | N | 3 | 4 | 7 | 3 | 4 | 7 |
| | | % | 42.9 | 57.1 | 100 | 42.9 | 57.1 | 100 |
| | Descending colon | N | 8 | 6 | 14 | 5 | 9 | 14 |
| | | % | 57.1 | 42.9 | 100 | 35.7 | 64.3 | 100 |
| | Transverse colon | N | 3 | 6 | 9 | 3 | 6 | 9 |
| | | % | 33.3 | 66.7 | 100 | 33.3 | 66.7 | 100 |
| | Rectosigmoid | N | 2 | 35 | 37 | 5 | 32 | 37 |
| | | % | 5.4 | 94.6 | 100 | 13.5 | 86.5 | 100 |
| | total | N | 16 | 51 | 67 | 16 | 51 | 67 |
| | | % | 23.9 | 76.1 | 100 | 23.9 | 76.1 | 100 |
| | **p-value** | | | 0.059 | | | 0.113 | |
| **Family history** | Positive | N | 7 | 34 | 41 | 7 | 34 | 41 |
| | | % | 17.1 | 82.9 | 100 | 17.1 | 82.9 | 100 |
| | Negative | N | 9 | 17 | 26 | 9 | 17 | 26 |
| | | % | 34.6 | 65.4 | 100 | 34.6 | 65.4 | 100 |
| | Total | N | 16 | 51 | 67 | 16 | 51 | 67 |
| | | % | 23.9 | 76.1 | 100 | 23.9 | 76.1 | 100 |
| | **p-value** | | | 0.101 | | | 0.101 | |

In the relationship between the gene expression of NRAS and Lymph vascular invasion using chi-square test, a significant relationship did not observe (p>0.05). According to Table 4, from 51 patients that in the terms of genes expression of NRAS were wild-type, 24 cases (47.1%) without Lymph vascular invasion and 27 (52.9%) had lymphovascular invasion. While there was a significant relationship between KRAS gene expression and lymphovascular invasion using chi-square test (p< 0.05).So that the highest rate of lymphovascular invasion in patients with mutations were observed in the gene KRAS.

In the study of gene expression NRAS and tumor grade, a significant relationship was found by using Fisher's test (p<0.05) and more than half of the patients who in terms of genes NRAS had mutations, in terms of tumor grade were in high stage. However, there was no significant relationship between KRAS gene expression and tumor grade using Fisher test (Table 4).

**Table 4.** The relationship between the expression of KRAS and NRAS genes with Lymphovascular invasion and tumor grade.

| Variable | | | Lymphovascular invasion | | | P | Tumor Grade | | | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | pos | neg | Total | | high | intermediate | low | Total | |
| NRAS | Wild | N | 27 | 24 | 51 | 0.817 | 24 | 15 | 12 | 51 | 0.022 |
| | | % | 52.9 | 47.1 | 100 | | 47.1 | 29.4 | 23.5 | 100 | |
| | None wild | N | 9 | 7 | 16 | | 14 | 1 | 1 | 16 | |
| | | % | 56.2 | 43.8 | 100 | | 87.5 | 6.3 | 6.3 | 100 | |
| | Total | N | 36 | 31 | 67 | | 38 | 16 | 13 | 67 | |
| | | % | 53.7 | 46.3 | 100 | | 56.7 | 23.9 | 19.4 | 100 | |
| KRAS | Wild | N | 23 | 28 | 51 | 0.011 | 26 | 14 | 11 | 51 | 0.264 |
| | | % | 45.1 | 54.9 | 100 | | 51 | 27.4 | 21.6 | 100 | |
| | None wild | N | 13 | 3 | 16 | | 12 | 2 | 2 | 16 | |
| | | % | 81.2 | 18.8 | 100 | | 75 | 12.5 | 12.5 | 100 | |
| | Total | N | 36 | 31 | 67 | | 38 | 16 | 13 | 67 | |
| | | % | 53.7 | 46.3 | 100 | | 56.7 | 23.9 | 19.4 | 100 | |

In comparing the TTP with the amount of NRAS and KRAS mutations, the results showed significant relationship of the TTP variables in both groups (p<0.05). Mean and standard deviation in wild and non-wild groups, in terms of NRAS genes were reported 10.8±4.7 and 8±3.2, while theses values for the gene KRAS were reported 10.76±4.3 and 8.13±5.0 respectively (Table 5).

**Table 5.** Investigation of the relationship between expression of KRAS and NRAS genes with TTP.

| Variable | | TTP | | | | | |
|---|---|---|---|---|---|---|---|
| | | N | Maximum | Minimum | Median | Mean ± Std | P-value |
| NRAS | Wild | 51 | 25 | 2 | 10 | 10.8±4.767 | 0.021 |
| | None-wild | 16 | 14 | 3 | 8 | 8±3.204 | |
| | Total | 67 | 25 | 2 | 10 | 10.13±4.582 | |
| KRAS | Wild | 51 | 25 | 2 | 10 | 10.76±4.302 | 0.009 |
| | None-wild | 16 | 24 | 3 | 7.5 | 8.13±5.005 | |
| | Total | 67 | 25 | 2 | 10 | 10.13±4.582 | |

## Discussion

KRAS and NRAS mutations are important in the carcinogenesis of CRC and play a certain role in the efficacy of anti-EGFR therapy (15, 16). Among the RAS family, mutations in KRAS account for about 85% and NRAS for about 15% of all RAS mutations in human tumors (17). NRAS is identical to KRAS in the first 85 amino acids. However, unlike KRAS, NRAS is not activated by specific cytokines or growth factors (18).

In this study evaluation of 67 patients infected with CRC showed that in terms of both KRAS and NRAS, 23.9% of patients, were not wild-type. The average age of patients was 58.67± 10.17 and in terms of gender distribution , 61.2% of the individual were men.

In the study of Palomba and et al that were performed on 1284 patients, the mean age of people was reported 64 years, and about 60% of them were male. Mutation in KRAS gene was 35.6% and in NRAS was 4.1% of patients that it was different from the values obtained in our study.Also, 35.1% of individuals were under 60 years old and 64.9% were over 60 (19). In the study of Kadowaki et al that were performed on 813 patients, mutation in KRAS gene were 38% of patients. Mean age of individuals in the mutation group for KRAS were reported 64.7 and in those without mutation were reported 63.5. In their study, 53% of the mutations were male and 47% were female (20). Also in the study Velho et al (21), 35.3% of patients had mutations in KRAS oncogene, Brink et al (2) also collectively reported the frequency of mutations in KRAS oncogene that took on 737 samples of patients with colorectal cancer (diagnosis age between 57 and 76 years old), 37% were reported. In the study of Kawazoe et al that carried out between 2013 to 2014 on 264 patients with metastatic colorectal cancer, mutations in KRAS ,NRAS, BRAF and PIK3CA genes were examined. KRAS gene mutation in 37.9% and NRAS gene mutation in 2.4% of patients were found. 64% of patients with a mutation in the RAS gene were men (22) .

In the current stud, in terms of the location of the primary lesion, in more than half of the samples (55.2%) rectosigmoid were reported that was almost similar to Kavazai study (54.3). While in the study of Palomba, the highest rate of sample (40 %) were related to the ascending colon. But in their study, the incidence of RAS mutations was not significantly different in each colon(19). In the study of Isnaldi etal also had involved in descending colon (69%) (23).

In the investigation of the relationship between genes expression in the NRAS and KRAS with age group, gender, lymphovascular invasion, tumor grade, family history, the location of primary lesion and TTP, no significant relationship were observed between incidence rate of NRAS and KRAS with age, family records and gender. But between gene expression rates of NRAS, there was a significant statistical relationship with the location of primary lesion. As in 57.1% of patients with the location of primary lesion in the descending colon, NRAS contained mutations and were reported not wild-type. Also, about expression of KRAS gene, significant relationship was found with lymph vascular invasion and tumor grade. The amount of lymphovascular invasion in patients with mutant KRAS and wild-type KRAS was 81.3% and 45.1% respectively and the highest rate of lymphovascular invasion has been observed in patients with mutations in the KRAS gene. According to our results, 87.5% of patients with the NRAS gene had mutations and in terms of tumors grade, they were at high stage. It should be noted that there was a significant relationship between the expression of both KRAS and NRAS genes with TTP.

In the study of Palomba et al (19) on 1284 patients with metastatic colon cancer, there was no statistically significant relationship between the mutation in the KRAS and NRAS genes and age, sex, location of the primary lesion, tumor grade variables. Whilst no significant relationship was found between the amount of mutations in NRAS and KRAS with overall survival and Time to progression. Along with our study, Zhang et al found that there is no significant relationship between mutations RAS and family history (24). About the relationship between lymphovascular invasion with gene mutation RAS, Sayagués et al stated that there was a significant relationship between KRAS mutations and right side colon tumor location and absence of lymph vascular invasion (25). ChangM.D et al also in their study of RAS family gene in CRC cancer stated that between three KRAS ,NRAS and HRAS genes, only mutation in KRAS gene with

lymphovascular invasion have significant relationship (26).

In parallel to our results, it was shown that in the Kawadawaki et al study that carried on 813 patients with colon cancer in Japan, it was reported that over 65 years of age ,male gender, and the existence of mutations in KRAS gene causes the worst prognosis and less survival. So that in the mutated state compared to no mutation, 5 years DFS (Disease free survival) were reported 71% versus 77% respectively and 5 years OS (overall survival) were reported 80% versus 84% respectively. But between KRAS genes and variables such as age and tumor stage, lymph node metastasis no statistically significant relationship was reported(20). Also in the study of Palomba et al examined the linked mutations in KRAS, NRAS, BRAF, and PIK3CA genes with sex, age at diagnosis, anatomical location of primary CRC, tumor grading variables, and reported that there was no significant relationship between the mentioned variables and the mutation in these 4 genes(19). In the study of Kawazoe that mutation in KRAS, NRAS, BRAF and PIK3CA were analyzed, although the mutation in the RAS genes in male sex, location of primary rectum tumor and well differentiation degree was more but no significant statistical relationship found. In their study was reported that mutations in any of the genes mentioned in PFS (Progression free survival) mutation group have less period (1.2-9.5 months) compared to those without the mutation (4.6-8.7months). While the OS (Overall Survival) disease in each of mutation group has less period than those without mutations (3.6-8.6 months vs 1.34-1.3 months) (22).

In the study of Jouini et al also the relationship between mutations in the RAS genes and variables such as age, gender ,age groups and perineural invasion, metastasis, vascular emboli and degree of differentiation was analyzed. In their study, mutations in the RAS genes have significant relationship with the degree of differentiation. 82% well differentiation patients have mutation in the RAS gene (14). In a meta-analysis by Therkildsen et al that carried on in 2014, was reported that mutations of both KRAS and NRAS genes with overall survival (OS) and progression-free survival (PFS) have less common disease and the existence of these mutations make them resistant to anti-EGFR drugs (27). Rebersek et al also stated in a study that median time to recurrence of the disease in patients after primary treatment of operable disease with a non-mutated *KRAS* gene was shorter than in patients with mutated *KRAS* gene (20 *vs*. 21 months), but the difference was not significant(28). In another study, Gasparini et al. express that the patients with wild-type tumors had a statistically significant better TTP as compared to those with *RAS* mutated disease with 7.4 ± .85 weeks versus 5.2 ± .91 weeks (29).

In general, there appears to be a mutation in the KRAS and NRAS gene can be used as a suitable biomarker for assessing response to targeted treatment. One of the limitations of this study was the expensive cost of the test and lack of samples despite of the analyze in a ten-year study due to the death and errors in patient records. It is thought that an increase in the sample size might affect the results and if the study carried on broad samples, better results can be achieved.

## Conclusions

Our study showed that the incidence rate of NRAS and KRAS have no relationship with age group, family history and gender, but patients whose primary lesion location was located in descending colon, the NRAS gene had a mutation. In addition, in more than half of the patients with NRAS mutations, the tumor grade was high. Also, the rate of lymphovascular invasion in patients without KRAS mutation, much less patients with mutation were reported. TTP was also lower in both KRAS and NRAS genes in patients with mutations than in non-mutated patients.

### Author contribution

**HSS** and **MMA** supervised and managed the project and also edited and revised the manuscript. **FN** and **KM** collected the data and wrote the primary draft of the manuscript.

### Conflict of interest

No potential conflict of interest was reported by the authors.

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# Prevalence of pressure ulcer and its related factors in elderly patients hospitalized to teaching hospitals in East Guilan

Zahra Razi-Chafi [1] , Mohammad Esmaeilpour-Bandboni [2] *, Zohreh Salmalian [2]

[1] Student Research Committee, Zeynab (P.B.U.H) School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

[2] Zeynab (P.B.U.H) School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

## Abstract

**Introduction:** Pressure ulcer is a pressure-induced tissue injury that can affect the skin, muscle, connective tissue, cartilage, and bone. Pressure ulcer is a painful, debilitating condition that endangers a person's health by increasing mortality and morbidity in terms of length of hospital stay, increasing the rate of infection, and the need for surgical procedures. Pressure ulcers are the third most expensive disease after cancer and cardiovascular diseases. About two-thirds of hospital beds are occupied by people over 65 years old. This study aimed to determine the prevalence of pressure ulcer and its related factors in elderly patients hospitalized at teaching hospitals in Guilan, Iran.

**Materials and Methods:** This was a descriptive cross-sectional study in which elderly patients who had been hospitalized for 24 hours or more in the intensive care units, internal and surgical wards of East Guilan educational hospitals were eligible for the study. Using the available stratified sampling method, 250 patients aged 60 years and older were included in our study. Data collection tools included socio-demographic and medical profile questionnaires and the Braden pressure ulcer risk assessment scale. Data were analyzed using SPSS version 22 statistical software. Descriptive statistics, Pearson correlation, Chi-square, and Fisher's exact tests were used to analyze data at a significant level of $P<0.05$.

**Results:** The prevalence of pressure ulcer in elderly patients hospitalized in teaching hospitals in was 26.4%. There was a significant relationship between the presence of pressure ulcer with age, length of hospital stay, type of ward, urinary and fecal incontinence, edema, level of consciousness, type of mattress used, connection to mechanical ventilation, position change, sensory perception areas, humidity, activity, and mobility. There was no significant relationship between the presence of pressure ulcer with gender, marital status, and surgical history.

**Conclusion:** Pressure ulcer has a high prevalence in hospitalized elderly and it is always accompanied by serious complications. it is better for nurses to check patients regularly and prevent its occurrence by controlling significant risk factors.

**Keywords:** Prevalence, Pressure ulcers, Elderly patients, Risk factors

*Corresponding Author: Mohammad Esmaeilpour-Bandboni

✉ Email: esmaeilmmm@yahoo.com

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## Introduction

The increase in the elderly population of the world, especially in Iran, has led to attention to the health of this age group. Research shows that about two-thirds of hospital beds are occupied by the elderly (people over 65) (1). According to studies and statistical indicators, it is predicted that the elderly population of Iran will reach 10.5% by 2025 and 21.7% by 2050 (2). One of the most important and common problems of hospitalized elderly patients, especially in intensive care units, is pressure ulcer, which causes many costs and complications for patients and the health system (3). pressure ulcers (also known as pressure sores, bed sores, or decubitus ulcers) are defined as localized skin lesions that result from the prolonged compression of the soft tissue between the inner bony part and the outer surface. Pressure ulcers occur in the elderly who are hospitalized for a long time. Aging is one of the risk factors for pressure ulcers (4). Decreased subcutaneous fat, skin elasticity and moisture, and dryness of the skin are some of the reasons for the increased risk of pressure ulcers in the elderly (5). Despite increasing awareness of the clinical consequences, and economic burden, the prevalence of pressure ulcers in the elderly hospitalized is high (6). According to epidemiological studies, the prevalence of pressure ulcers in European hospitals was between 8.2 to 23%, and 12.3% in US hospitals (7). In Iran, the prevalence of pressure ulcers is between 10.1 to 21% in special wards, and 5% in general wards (8). In 2012, Theisen et al. reported a pressure ulcer prevalence of 7.1% in elderly patients of a German University Hospital (9). In addition to physical and mental problems in elderly patients, pressure ulcers cause loss of function and increase the incidence of infection, and the length of hospital stay and as a result increase economic cost. Therefore, prevention of pressure ulcers is the most effective measure. The incidence of pressure ulcers is a major and important indicator of good nursing care. The nurse is the first health care person who can prevent the occurrence of many pressure ulcers among elderly with her (his) good intervention (10). In an overview, no comprehensive study has been conducted in Guilan province, as the oldest province in Iran, regarding the estimation of the prevalence of pressure ulcers in elderly patients. Considering the disability and mortality caused by pressure ulcers, as well as the high cost of treatment, knowing the prevalence of pressure ulcers and its' risk factors can be useful especially in nursing. Therefore, this study aimed to determine the prevalence of pressure ulcers and related factors in the elderly hospitalized in East Guilan hospitals.

## Materials and Methods

This descriptive cross-sectional study, from April until July 2021, 250 elderly people were selected from 6 hospitals affiliated to Guilan University of Medical Sciences in northern Iran using the available stratified sampling method. Criteria for inclusion in this study are the elderly aged at least 60 years and older hospitalized in the intensive care units and internal and surgery wards of selected hospitals that have been admitted for at least 24 hours. The presence or absence of pressure ulcers and the degree of ulcers were evaluated and the possibility of pressure ulcers was assessed based on the Braden scale. The data collection tool had three parts. The first part was related to personal-social and medical characteristics includes: hospital name, gender, age, marital status, length of hospital stays, and type of ward. Medical characteristics, including diagnosis, presence of underlying diseases (heart failure, respiratory failure, renal failure, multiple organ failure, hypertension, diabetes), urinary and fecal incontinence, edema, patient level of consciousness, type of mattress used, connection to the mechanical ventilator and the duration of connection, recent surgery, change of position, limb casting and having traction.The level of contiousness was assessed by Glaco Coma scale, this scale evaluate three domain, eye opening, best verbal response, and the best motor function. The score of this scale is at least 3 to maximum 15. The second part was the observational checklist to examine the common sites for pressure ulcers such as the back, shoulders, Iliac crest, trochanter, sacrum, buttocks, the side edge of the foot, heel, neck, and other sites. The third section was Braden Predictive Scale, which is used to diagnose patients at risk for pressure ulcers. This scale includes 6 subsets of sensory perception, moisture, activity, mobility, nutrition, and Stretch or wear. The range of scoring is from 6 to a maximum of 23. Therefore, a score of ≥15 indicates low risk, 13 to 14 moderate risk, 10 to 12 high risk, and ≤9 very high risk for pressure ulcer. Finally, the data were analyzed by using SPSS

version 22 statistical software. A Kolmogorov - Smirnov test indicated that the data was sampled from a population with a normal distribution. Descriptive statistics (mean and standard deviation), Pearson correlation, Chi-square, and Fisher's exact tests were used to measure the relationship between demographic variables and Braden tool score according to abnormal or normal variable distribution, at a significance level of $P<0.05$.

### Ethical Consideration

In this study, the principles of research ethics were considered based on the latest version of the Helsinki Declaration. Informed consent was obtained from all patients. For those patients who were unable to communicate, had a reduced level of consciousness or were connected to the Ventilator, informed consent was obtained from their families. In addition, this is the nursing thesis at the MSN level and was approved by Guilan University of Medical Sciences Ethical Committee with the ethical code IR.GUMS.REC.1398.461.

## Results

Our findings revealed that the prevalence of pressure ulcers in elderly patients was 26.4%. Most of the elderly had first (46.1%) and second (44.15%) degree pressure ulcers (Table 1) and the most common sites of pressure ulcers were sacrum (29.22%), hip (26.62%), and heel (14.28%) (Table 2). The mean age of the patients was calculated to be 69.54 ± 9.33 years, and 59.6% of the cases were male. Findings revealed that 99% of the patients had less than 10 days of hospitalization. The results of this study showed that there is a significant relationship between age and the prevalence of pressure ulcers in hospitalized elderly (P-value ≤ 0.05), and the prevalence of pressure ulcer increased with age. However, there was no significant relationship between gender and the prevalence of pressure ulcers.

**Table 1.** Frequency distribution and percentage of pressure ulcers based on demographic variables and Braden Scale.

| Variable | Category | Frequency | Percent |
|---|---|---|---|
| **Duration of Hospitalization** | 10 days and less than 10 days | 248 | 99.2 |
| | More than 10 days | 2 | 0.8 |
| **Inpatient department** | CCU | 27 | 10.8 |
| | ICU | 65 | 26 |
| | Internal | 72 | 28.8 |
| | Surgery | 86 | 34.4 |
| **Existence of underlying disease** | Yes | 201 | 80.4 |
| | No | 49 | 19.6 |
| **Urinary incontinence** | Yes | 63 | 25.4 |
| | No | 187 | 74.8 |
| **Stool incontinence** | yes | 61 | 24.4 |
| | No | 189 | 75.6 |
| **Edema** | Yes | 39 | 15.6 |
| | No | 211 | 84.4 |
| **Level of consciousness** | Less than 10 | 30 | 12 |
| | 10 to 14 | 56 | 22.4 |
| | 15 | 164 | 65.6 |
| **Type of mattress** | Wave | 100 | 40 |
| | Normal | 150 | 60 |
| **Connect to ventilator** | Yes | 23 | 9.2 |
| | No | 227 | 90.8 |
| **Surgery** | Yes | 81 | 32.4 |
| | No | 169 | 67.6 |
| **Braden scale score** | Very high risk ≤ 9 | 29 | 11.6 |
| | High risk (10 - 12) | 49 | 19.6 |
| | Moderate risk (13 - 14) | 80 | 32 |
| | Low risk (15 – 18) | 46 | 18.4 |
| | Normal control ≥ 19 | 46 | 18.4 |
| **Existence of pressure sores** | Yes | 66 | 26.4 |
| | No | 184 | 73.6 |
| **Degree of pressure ulcer** | Degree 1 | 71 | 46.1 |
| | Degree 2 | 68 | 44.15 |
| | Degree 3 | 11 | 7.14 |
| | Degree 4 | 4 | 2.59 |

**Table 2.** Frequency of pressure ulcer site in the elderly under study.

| Site of pressure ulcer | Percent | Frequency |
|---|---|---|
| **Behind** | 0.65 | 1 |
| **Shoulder** | 5.19 | 8 |
| **Iliac crest** | 5.84 | 9 |
| **Trochanter** | 11.03 | 17 |
| **Sacrum** | 29.22 | 45 |
| **Side edge of the foot** | 3.24 | 5 |
| **Heel** | 14.28 | 22 |
| **Buttocks** | 26.62 | 41 |
| **Neck** | 0.65 | 1 |
| **Other** | 3.24 | 5 |
| **Total** | 100% | 154 |

In addition, it was shown that there was a significant relationship between the prevalence of pressure ulcers in elderly patients with the duration of hospitalization, decreased level of consciousness, type of hospitalized ward, connection to a ventilator, limb edema, urinary and fecal incontinence, and sensory perception impairment ($p \leq 0.05$). The highest prevalence of pressure ulcers was observed in intensive care units (60%). The findings related to determining the causes of pressure ulcers based on Braden criteria are as follows:

Using Chi-square and Fisher's exact test, there was a significant relationship between the prevalence of pressure ulcers with sensory perception impairment, skin moisture, the need for moderate to high assistance in shaking, and limited physical activity of the elderly patient (P<0/05). The prevalence of pressure ulcers was higher in the elderly who were completely immobile or had very limited mobility. In general, examination of samples based on the Braden tools showed that about 31.2% of the hospitalized elderly are at high risk of developing pressure ulcers (Table 3).

**Table 3.** Frequency and determining the relationship between the prevalence of pressure ulcers and Braden scale in the elderly under study.

| Braden scale | Pressure ulcer | | P-Value |
|---|---|---|---|
| | With pressure ulcer (Percent) | Without pressure ulcer (Percent) | |
| **Very high risk** | 28 (96.6%) | 1 (3.4%) | **P<0.001** |
| **High risk** | 36 (73.5% ) | 13 (26.5%) | |
| **Moderate risk** | 2 (2.5%) | 78 (97.5%) | |
| **Low risk** | 0 (0%) | 46 (100%) | |
| **Normal control** | 0 (0%) | 46 (100%) | |
| **Total** | 66 | 184 | |

## Discussion

In the present study, the prevalence of pressure ulcers in the elderly was 26.4%. Out of 250 hospitalized elderly, 66 had pressure ulcers. The findings of the study are consistent with the results of the meta-analysis conducted by Karimian et al., in which the prevalence of pressure ulcers was reported to be 19% in Iran (11). In the study of Bereded et al., the prevalence of pressure ulcers was 14.9% (12). The overall prevalence of bed sore in the study of Assefa et al. was 9.6% (13). Discrepancies in the results of studies may be due to factors such as nursing services and sample size, study duration, sampling method, and type of study.

In this study, most of the elderly had first- and second-degree pressure ulcers. In the study of Mobayen et al., most patients had grade 2 or grade 3 ulcers (4). Shokati Ahmadabad et al. showed that 41.4% and 4.3% of the patients in their study had grade 1 and grade 2 ulcers, respectively (14). In the present study, the most common site with pressure ulcers was the sacrum (29.22%). The findings of the study are consistent with the results of the study of Ayyıldız et al., where the prevalence of pressure ulcers in the sacrum was higher (78.8%) (15). As we know, the sacrum of elderly patients bears the most weight, and as a result, is reported as the most common place for pressure ulcers.

Based on the research findings, a significant relationship has been established between age and the prevalence of pressure ulcers. The findings of the study are consistent with the results of the study of Ayyıldız

et al. in which the most important risk factor for the development of pressure ulcers was found to be advanced age (15). In the study of Mobayen et al. and Walther et al., increasing age had a significant effect on the development of pressure ulcers, so most cases of pressure ulcers were observed in patients over 60 years (4,16). Karimian et al. reported that the highest and lowest prevalence of pressure ulcers in Iran belonged to the age groups of 60-70 and 40-50 years with prevalence rates of 22% and 14%, respectively, suggesting that the incidence of pressure ulcer increases with age (11). The results of a study performed by Arba et al. indicated that increasing age was significantly associated with the prevalence of pressure ulcers. (3). Elderly people seem to have wrinkled skin due to subcutaneous fat loss and are prone to pressure ulcers.

Also in this study, the length of hospital stay is involved in the prevalence of pressure ulcers. But Assefa et al. reported that the length of hospital stay was not associated with the occurrence of pressure sore (13). In the study of Mobayen et al., the length of hospital stay was influential in the prevalence of pressure ulcers (4). Prolonged hospitalization increases the risk of pressure ulcers (17). In a study conducted by Bereded et al. on 355 hospitalized adult patients, it was reported that length of stay was significantly associated with pressure ulcer. Patients whose length of stay was 7–20 days were 8.44 times more likely to develop pressure ulcer than patients who stayed for ≤ 6 days. When the length of hospital stays increases, the risk of hospital-acquired infection increases which leads to the development of pressure ulcer (12). Staying in the hospital, especially in the intensive care unit, due to the restriction on the patient's activity, without considering other factors, has the greatest impact on the development of pressure ulcers. However, pressure ulcers themselves may also prolong the patient's stay (18).

Findings show that a significant relationship was established between the prevalence of pressure ulcers and the level of consciousness of the elderly. The prevalence of pressure ulcers was higher in the elderly with lower levels of consciousness. The findings of this study are consistent with the results of the study of Ayyıldız et al. in which decreased level of consciousness and nutritional problems in elderly patients has been one of the effective factors in the development of pressure ulcers (15). Mobayen et al. wrote in this regard: Patients with a level of consciousness less than 8 have a higher incidence of pressure (4). According the results of Akarsu Ayazoglu et al., patients with lower level of consciousness had less sensory perception Just like the patient under anesthesia or sedation, in this condition, the patient's skin is under pressure for a longer time. They cannot perceive pain from severe stress or change their position independently or request a change of position (18). In this study, most of the elderly who suffered from pressure ulcers were hospitalized in the intensive care unit and had a lower level of consciousness and sensory perception, therefore, the prevalence of pressure ulcers was higher.

This study showed that the prevalence of pressure ulcers was higher in the elderly who were physically confined to bed. There was a significant relationship between the prevalence of pressure ulcer and the activity of the elderly patient. Assefa et al. concluded that patients whose physical activity has been reduced are more likely to suffer from pressure ulcers (13). In studies conducted by Bereded et al. and Ippolito et al., it was found that activity was significantly associated with pressure ulcer. Patients dependent on a wheelchair or bed, were 11 times more likely to develop pressure ulcer than those patients who walked frequently (12,19).

According to the Braden scale, only 17 elderly patients were completely immobile. The prevalence of pressure ulcers was higher in the elderly who were completely immobile or very limited in terms of mobility. There was a significant relationship between the prevalence of pressure ulcers and the mobility of the elderly.

Assefa et al. reported impaired mobility as one of the effective factors in causing pressure ulcers (13). Bereded et al. wrote: Patient’s position change was also the other independent variable which was significantly associated with pressure ulcer. Those patients who did not have their position changed were 10.42 times more likely to develop pressure ulcer than those who had their position changed every 2–3 h (12). The prevalence of pressure ulcers in the elderly admitted to the intensive care unit was higher than in other wards, because they have more limited in movement.

Therefore, they will be more prone to pressure ulcers. It is obvious that the elderly who have been immobile for a long time, have limited movement, or change their position slowly, the muscle tissues are placed between the bony ridges and the mattress for a longer period of time, and as a result, the prevalence of bedsores is higher. Inadequate nutrition in elderly patients is one of the effective factors in causing pressure ulcers (15). Nadukkandiyil et al. and Ayyıldız et al reported that one of the most important factors in the development of pressure ulcers, especially in elderly patients, is malnutrition (10, 15).

The results of this study showed that the risk factors for pressure ulcers in the elderly admitted to hospitals are old age, decreased activity and mobility, decreased level of consciousness, inadequate nutrition, and long hospital stay.

## Conclusions

As it was observed, there were many effective factors in the development of pressure ulcers in the elderly, so it is the responsibility of nurses to prevent the spread of pressure ulcers by identifying susceptible and at-risk elderly patients before the occurrence of this complication or to prevent the transformation of first-degree wounds into higher-grade wounds by implementing appropriate nursing measures. In addition, according to the priority of prevention over treatment, it is recommended that in hospital wards, especially intensive care unit, elderly should be regularly observed and assessed by nurses to prevent pressure ulcers.

### Author contribution

**ZRCh** collected data and provided draft of manuscript, **MEB** performed the analysis and wrote the paper, **ZS** collected data and coordinated the administrative work.

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### Conflict of interest

No potential conflict of interest was reported by the authors.

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# Evaluation of dermoscopic findings of longitudinal melanonychia in referred patients to dermatology clinics in Guilan, Iran

Kaveh Gharaei Nejad [1], Hojat Eftekhari [1]*, Abbas Darjani [1], Narges Alizadeh [1], Rana Rafiei [1], Reyhaneh Ghadarjani [2], Mitra Elyasi [3], Negin Pour-Shahidi [1]

[1] Skin Research Center, Razi Hospital, Guilan University of Medical Sciences (GUMS), Rasht, Iran

[2] Department of Pathology, Razi Hospital, Guilan University of Medical Sciences (GUMS), Rasht, Iran

[3] Department of Pediatrics, School of Medicine, Pediatrics Research Center,17 Shahrivar Hospital, Guilan University of Medical Sciences (GUMS), Rasht, Iran

## Abstract

**Introduction:** Longitudinal melanonychia (LM) is a common clinical condition that is mostly identified by the presence of longitudinal, demarcated, and pigmented bands on the nail. Different benign or malignant pathologies can present with longitudinal melanonychia. Therefore, we aimed to investigate the frequency of dermoscopic features of LM in patients with LM referred to dermatology clinics in Guilan, Iran.

**Materials and Methods:** This case-series study was conducted on 30 patients with LM who were referred to Besat clinic and Razi hospital, Rasht, Iran, from March 2022 to August 2022 with a complaint of LM. Demographical data and dermoscopic findings of patients were collected and analyzed using SPSS version 21. The LM and dermoscopic features were investigated using a dermatoscope (HEINE IC1, HEINE Optotechnik, Germany).

**Results:** Out of 30 patients, 24 patients were female and 6 patients were male with a mean age of 30.08 ± 14.31 years old. Among these patients, five patients had a family history of LM, one patient with melanoma had Hutchinson's sign, and three patients had pseudo-Hutchinson's sign. The mean width of lesions of the nail was 2.42±2.12 mm with a mean time of onset of 7.42 ± 7.12 months. Also, the majority of the involved site of LM was hand (26.6%).

**Conclusion:** According to our study, LM was more frequent in females and the trauma-related lesions of the nail were the most common dermatological findings among the patients.

**Keywords:** Dermoscopic findings, Linear melanonychia, Melanoma

***Corresponding Author:** Hojat Eftekhari

✉ Email: hojat.eftekhari.derm@gmail.com

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## Introduction

Longitudinal melanonychia (LM) is identified by the presence of longitudinal, demarcated, and pigmented bands on the nail (1)**.** The frequency of LM has been reported variously according to age groups, ethnicity, and gender (2–5). Melanonychia is characterized by brownish-black discoloration of the nail plate. In fewer cases, this color change can also be seen transversely from light brown to blue-black and it is called transverse melanonychia. Melanonychia may also involve the entire nail plate, which is referred to as total melanonychia (6). The width of these lines can vary from a few millimeters (mm)s to those that cover the entire nail plate (7,8).

LM is a product of melanin deposition in the nail plate, which is created by the melanocytes of the nail matrix (9). The etiology of LM is categorized as melanocytic activation or melanocytic hyperplasia (benign nail matrix nevi and malignant subungual melanoma) (10). Subungual melanoma can initially appear as LM. Subungual melanoma is a malignant neoplasm that requires early diagnosis and complete surgical excision and it has an increasing trend in Guilan, Iran (11). Malignant melanoma accounts for *7*5% of all skin cancer deaths and is potentially curable in the case of early diagnosis (12). Hutchinson's sign, which indicates the radial growth phase of the tumor, is highly suggestive of nail melanoma but may be absent in primary or *in situ* lesions (13). Different etiologies of LM can be differentiated by biopsy and histopathological examination but nail biopsy is an aggressive and costly procedure that can cause irreversible dystrophy of the nail plate, therefore, the physician should be cautious about performing this procedure.

Dermoscopy is a non-invasive and inexpensive method in which, by attaching a camera to a magnifying set of lenses, enables the practitioner to better evaluate the epidermis, upper dermis, superficial vascular structures and pigmentations with 10-50 × magnification. Although used primarily for pigmentary lesions (e.g. melanocytic nevi), dermoscopy can be helpful in assessing non-pigmented lesions and inflammatory processes like lichen planus of scalp (14,15). While the gold standard diagnosis method is nail biopsy, dermoscopy is a useful noninvasive method to investigate various dermatological disorders and provides important information for the management of melanonychia, which can help to avoid unnecessary nail biopsies (16–18). Although dermoscopy has limitations in providing direct analysis of the nail matrix and pigment band origins, still it is an integral part of the clinical evaluation of LM (19–21).

Since LM is always one of the most challenging complaints in dermatology clinics, and acral lentiginous melanoma (ALM) is one of the sub-branches of melanoma that can represent a melanotic pattern, which is hardly diagnosed, the early and accurate diagnosis of these complications is vital. In this regard, we aimed to investigate the dermoscopic features of LM in patients via dermatoscope to prevent unnecessary nail biopsy in these patients.

## Materials and Methods

### Study design and variables

In this case-series study, demographical data and clinical characteristics of 30 patients with complaints of LM or diagnosed by LM at the time of entrance who were referred to the dermatology unit of Besat clinic and Razi hospital, Rasht, Iran, from December 2020 to August 2020, were collected. The data included age, gender, the time of the onset, family history of melanoma, family history of melanonychia, drug history (with a focus on the drug which may cause LM), history of trauma of the nail, the irregular margin of the LM, frequency of multicolor (polychromasia) in LM, presence of Hutchinson’s sign (when melanin pigment extends into the skin and soft tissue surrounding the nail plate, such as hyponychium, eponychium, or lateral grooves) (22) and pseudo-Hutchinson’s sign, subungual hyperkeratosis, dystrophy of the nail surface, onycholysis, number of fingers involved, and width of the pigmented band. LM was evaluated using a hand-held dermatoscope (HEINE IC1, HEINE Optotechnik, Germany) with ×10 magnification. In the case of suspicious manifestations in favor of malignancy, the biopsy of the nail was taken for further investigations. The exclusion criteria included patients with incomplete data**.**

### Statistical analyses

Mean and standard deviations are used to describe quantitative variables with normal distribution. Qualitative variables are described using numbers and percentages. Statistical calculations were performed using the IBM SPSS Statistics version 21.

## Results

Clinical data of 30 patients with LM were analyzed. The majority of the study population consisted of females (80%), the mean age of patients was 30.08±14.31 years old with no family history of melanoma, while 16.6% of patients had a family history of LM. Polychromatic lesions and lesions with irregular margins were detected in four patients. Hutchinson's sign was only present in one patient and three patients had pseudo-Hutchinson's sign. Subungual hyperkeratosis, drug-induced melanonychia, and dystrophy were rare among patients. Nevertheless, trauma-related melanonychia was reported in 40% of patients with LM. The mean width of the pigmented lesion was 2.42±2.12 mm (4.45-0.30 mm) with a mean duration of 7.42±7.12 months (0.3-14.5 months). The frequency of clinical manifestation of LM is illustrated in table 1.

**Table 1.** The frequency of demographical data and dermatological manifestation of patients with Longitudinal melanonychia.

| Variables | | Number (%) |
|---|---|---|
| **Age (year)** | <15 | 4 (13.33) |
| | 15-30 | 9 (30) |
| | 30-45 | 15 (50.66) |
| | 45< | 2 (6.66) |
| **Gender** | Male | 6 (20.00) |
| | Female | 24 (80.00) |
| **Family history of melanoma** | Yes | 0 (0.00) |
| | No | 30 (100.00) |
| **Family history of melanonychia** | Yes | 5 (16.66) |
| | No | 25 (83.33) |
| **Polychromatic lesion of nail** | Yes | 4 (13.33) |
| | No | 26 (86.66) |
| **Nail's lesion with irregular margin** | Yes | 4 (13.33) |
| | No | 26 (86.66) |
| **Hutchinson's sign** | Yes | 1 (3.33) |
| | No | 29 (96.66) |
| **Pseudo- Hutchinson's sign** | Yes | 3 (10.00) |
| | No | 27 (90.00) |
| **History of trauma** | Yes | 12 (40.00) |
| | No | 18 (60.00) |
| **Subungual hyperkeratosis** | Yes | 1 (3.33) |
| | No | 29 (96.66) |
| **Onycholysis** | Yes | 5 (16.66) |
| | No | 25 (83.33) |
| **Dystrophy** | Yes | 2 (6.66) |
| | No | 28 (93.33) |
| ***Drug*-induced *melanonychia*** | Yes | 2 (6.66) |
| | No | 28 (93.33) |
| **Fingernails and toenails involvement** | Thumb | 11 (36.66) |
| | Index | 5 (16.66) |
| | Multiple fingernails | 8 (26.66) |
| | Multiple toenails | 2 (6.66) |
| | Multiple fingernails & toenails | 4 (13.33) |

## Discussion

Melanonychia could be an important sign for a variety of benign or malignant nail diseases, and the differential diagnosis of LM from melanoma is important for dermatologists (7,9,23,24). Subungual melanoma can mimic onychomycosis or paronychia, leading to a delay in diagnosis since pigmented longitudinal bands within the nail plate can be seen in some benign lesions of the nail (25,26).

Our results showed a higher frequency of LM among patients of the female gender, aged 30-45 years old. The frequency of LM varies according to the different geographical regions. In a recent study conducted by Signal and Bisherwal, the prevalence of LM was estimated to be about 4.1% in the age group of 56-65 years (7); while Sobjanek et al. reported that the frequency of LM was 19.4% with the majority in the age group of 49 years (4). Leung et al. reported that the prevalence of LM was 0.8% with equal frequency among males and females (3), which was in contrast to our results, which have been demonstrated to be more frequent in females.

In this present study, a family history of LM was reported in 16.6% of patients but no history of melanoma has been identified. The frequency of

polychromatic, lesions with irregular margins, Hutchinson and pseudo-Hutchinson's sign, sublingual hyperkeratosis, onycholysis, dystrophy, and drug-induced lesions of the nail was less than 15% among patients. Only one patient had melanoma based on the dermoscopy findings that represented an irregular and polychromatic lesion along with Hutchinson's sign with the biopsy confirmation of melanoma.

A study by Ko BS et al. illustrated that none of the patients with subungual melanoma had a personal history of melanoma and one of the eight patients with subungual melanoma had a family history of melanoma (27). Moulonguet et al. reported that Hutchinson's sign and nail dystrophy were identified in 40% of patients with melanoma, while it was reported in only 3.5% of patients with benign lesions (28). Moreover, in the present study, the frequency of pseudo-Hutchinson's sign was reported to be 10% in patients with LM, therefore, follow-up of patients every six months was recommended.

It has been reported that the most common causes of LM with melanocyte hyperplasia are subungual melanoma, melanocytic nevus, and lentigo simplex (29). Alessandrini et al. reported in their study on dermoscopy findings on 100 patients with LM that six patients had melanocytic activation, 22 patients had nail matrix nevi, eight patients had melanocytic hyperplasia, and five patients had melanoma. Also, drug-induced lesions were reported in 8% of patients with LM. Furthermore, they reported that the most common fingers of involvement were the thumb, index finger, fingernails, multiple fingernails & toenails, and toenails, respectively (30), which was similar to our results.

Due to the present study, the mean width of the pigmented lesion was reported 2.42 mm in diameter with the most frequency in the thumb, multiple fingernails, index finger, multiple fingernails and toenails, and multiple toenails, respectively. Rodger et al. reported that the mean width of lesions in patients with LM was 6.2 mm, which was different from our results. The number of involved nails and the width diameter of the lesions vary due to different factors, in which drug exposure, co-existence of other dermatological diseases, and racial pigmentation commonly result in multiple nails, while lentiginous and nail matrix nevus results in single nail involvement (17,19,31,32).

## Limitation

The limitations of our study were the failure to perform long-term follow-up of the pigmented lesion to ensure whether the lesion is benign or not by considering the history of underlying disease. Also, it should be considered that a dermatoscope, like any other diagnostic tool, may miss the diagnosis of some samples.

## Conclusions

Melanonychia is a challenging dermatological symptom for specialists, in this regard, nail dermoscopy is an important method in the diagnosis of melanosis and allows to avoidance of unnecessary biopsies for LM.

### Author contribution

**KGH** and **HE** participated in the research design and writing the first draft; **RGH**, **AD**, and **RR** participated in the performance of the research and analytic tools; **NA**, **ME**, and **NP** participated in data analysis. All author reviewed and confirmed the final manuscript.

### Ethical approval

This study design was approved by the ethical committee of Guilan University of Medical Sciences (IR.GUMS.REC.1400.503).

### Conflict of interest

No potential conflict of interest was reported by the authors.

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# Comparative study of virtual and traditional teaching methods on the theoretical course of ECG in medical students of emergency department

Seyyed Mahdi Zia Ziabari [1], Zoheir Reihanian [2], Masoumeh Faghani [3] *, Nazanin Noori Roodsari [4], Ashkan kheyrjouei [4], Rasoul Tabari Khomeiran [5], Ehsan Kazemnezhad Leyli [6]

[1] Department of Emergency Medicine, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2] Road Trauma Research Center, Department of Neurosurgery, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[3] Department of Anatomical Sciences, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[4] Clinical Research Development Unit, Poursina Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[5] Department of Medical Surgical Nursing, School of Nursing and Midwifery, Social Determinants of Health Research Center, Guilan University of Medical Sciences

[6] Department of Biostatistics, School of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran

## Abstract

**Introduction:** The emergency ward is one of the most important parts of the hospital, where people's activities can have many effects on the performance of other wards of the hospital and the satisfaction of patients. Changing lifestyle and transformation of cyberspace into one of the pillars of modern life has had a great impact on learning and teaching methods. To compare the level of theoretical emergency learning in medical students with two virtual and traditional methods.

**Materials and Methods:** This quasi-experimental study was conducted on 88 medical students who started their emergency rotation in two hospitals of Guilan University of Medical sciences in 2021. Both groups participated in the same exam before and after the basics of electrocardiogram (ECG), normal ECG, types of blocks, diagnosis of MI and arrhythmias education. After collecting the information from the questionnaires, the data analysis was performed via SPSS software with a significant $P<0.05$.

**Results:** Out of 88 students, 56.8% were female, and 43.2% were male. The mean and median knowledge score before and after education was statistically significant in two groups ($P<0.001$). The virtual group represented a higher average score of knowledge than the traditional group. The student' grade point average affected the result of the score after education ($P=0.019$, $\beta=0.234$).

**Conclusion:** The use of virtual education methods in combination with traditional methods might help to improve the learning process and knowledge of medical students in emergency department.

**Keywords:** Clinical education, WhatsApp, Emergency course, Medical students

*Corresponding Author: Masoumeh Faghani

✉ Email: mfaghani@gums.ac.ir

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## Introduction

Clinical education is important for medical students' curriculum (1). Medical students learn in theory and bedside in hospitals. Based on the curriculum, students enter the different clinical departments and pass their education periods in the form of traditional classes of theory and clinical rounds (2).

Correct treatment in the emergency ward has an effect on the satisfaction of patients and the function of another ward of the hospital (3). The admission of people in the hospital often happens in the emergency ward for their needs and urgent care, so understanding their problems in this ward is essential (4). In addition, in the emergency ward, the student faces a large volume of clients with different clinical complaints, stable and unstable problems, and a wide range of acute and chronic diseases, so it is necessary to receive related training to deal with them (5). During this part of the medical student's curriculum, under the supervision of emergency medicine faculty members, they will learn how to take a history, examine and perform diagnostic and therapeutic procedures (6). Generally, they learn the main approach for treatment in an emergency situation, pay attention to the patient's main complaint, and acquire necessary abilities to face common referrals.

Clinical learning in general medicine is divided into two parts. In physiopathology, students focus on learning about the diagnosis and pathology of diseases. In the internship and intership, courses focus on the management and treatment of the disease (7). Hospital-based clerkship is a good opportunity for medical students to learn treat patients by combining theoretical and clinical knowledge in the hospital environment under the supervision of professors (6). The Covid-19 pandemic provided an opportunity for professors to make better use of virtual education and teach virtually where the presence of students in the hospital is not required (8,9).

In the learning process, teaching and learning are interdependent. Effective teaching can increase the quality of learning in students (10). Introducing new approaches and attitudes to education, including blended learning (BL), can be essential in resolving this issue. BL introduced as a learning method includes traditional and a variety of methods with specific technologies. BL is a combination of different methods of communication with technologies such as electronic learning (e-learning), e-performance support, and knowledge management practices for providing education (11,12). BL was first formally introduced by Marsh in 2003. Some consider BL as a combination of traditional and e-learning methods. Researchers showed that it as a suitable approach to achieve the desired learning goals by using appropriate technology and tailored to learning styles (13). Nowadays, virtual e-learning is considered the most advanced educational method that uses advanced technologies through electronic services (14,15).

The hospital environment is one of the most interactive work environments(16). The interactions between health workers with patients and themselves can lead to learning and experience of human resources (17). So, learning is the way to create student work and improve efficiency in an organization like a hospital. Since an organization can achieve its goals through capable employees, and it might enhance through learning. In addition, the prevalence of heart patients in the emergency ward is noticeable. It is necessary for students to learn the basics of electrocardiogram (ECG), normal ECG, types of blocks, diagnosis of MI and arrhythmia in order to examine heart patients who go to the emergency ward of the hospital. Therefore, due to the high importance of learning and achieving the best method of ECG education, we conducted a study to compare virtual and traditional education of theoretical knowledge of ECG in medical students of the emergency ward.

## Materials and Methods

### Data collecting

This quasi-experimental study was approved by the Ethics Committees of Guilan University of Medical Sciences (number: IR.GUMS.REC.1399.548). The inclusion criteria were: 1- Medical students of Guilan University of Medical Sciences who have passed the pre-internship exam. 2- Signing the consent form to participate in the study. Participating are 88 medical students in their 6th educational years. The sample size was designed with 5% error probability, 95% reliability and 0.5 relative frequency based on the results of the

study by Shaw et al(18). The medical students started their emergency medicine rotation in Poursina and Razi hospitals, in the second semester 2020-2021.

Based on the study design, these medical students divided randomly in two traditional and virtual education groups. The basics of electrocardiogram (ECG), normal ECG, types of blocks, diagnosis of MI and arrhythmia were taught in traditional and virtual classes for two traditional and virtual groups of interns in the emergency ward. The first group (traditional education=44), which included students that entered the emergency unit in three consecutive courses, was first given personal and educational information. Then, they were taught in a classroom, where students sat together for one session and attended an ECG analysis class. Several ECGs were provided to the students and explained in groups by solving problems. For the second group (virtual: n=44), which was the students of next three educational courses (one month after traditional group), the educational materials and slides related to the ECG were provided in the WhatsApp group (a messaging application).

The research tool was a questionnaire that designed for this research. Questionnaire questions were designed as multiple choice based on the diagnosis of normal ECG and emergency heart diseases. The faculty members of medical schools in Guilan University of Medical Sciences designed this two-part questionnaire. The first part of questionnaire included medical student's demographic such as age, gender, grade point average of previous years of students. The second part of questionnaire was consisted fifteen questions about student knowledge related to normal ECG, types of blocks, diagnosis of MI and arrhythmia. Before and three days after the education, the students of each group were tested via the same questionnaire.

The content validity of questionnaire was approved via the opinions of a panel of 10 experts of faculty members. Using Lawshe rule of content validity; all items had a value more than 0.62. Also all questions had a Content Validity Index (CVI) of 90% or higher. The maximum score of student awareness was between 0 to 8. The scores below 33.3% were considered poor, between 33.3% to 66.6% as average, and scores above 66.6% as excellent knowledge category.

**Statistical analysis**

The data were analyzed using SPSS. The mean, standard deviation (SD), minimum and maximum with a 95% confidence interval (CI) used to determine the learning rate of medical students in the two educational groups. We used the frequency and percentage to determine of learning status (poor, moderate, good). Paired T-test was done to compare the scores before and after the test, and Independent T-test was done to compare the score changes. Analysis of covariance was used to determine the difference of two groups by controlling the variables of grade point average, previous score, gender, and age group. Also, the Chi-square test was used to compare the performance of learning status with a significant level of $P < 0.05$.

## Results

Data from demographic part of questionnaire revealed that the medical students had an age range of 24-26 years (mean 24.5±0.66), 43.2% of males (n= 38), 56.8% females (n = 50). There was no significant difference in the frequency distribution of gender (P=0.667) and age (P=0.131) between two studied groups with Chi Square test. Because the number of medical students introduced to the ward is determined directly by the medical school, all students were included in the study. The mean students' grade point average (GPA) was 15.1 ± 4.35 in traditional and 15.1 ± 34.27 in virtual groups. Independent t test revealed that there were not statistically significant differences between the mean of GPA in the medical students of two groups (P=0.808).

Mann Whitney U Test was used for comparison of knowledge score before and after three days of education in two groups (Figure 1). A statistically significant differences was found between groups (P= 0.001) and in each group (P<0.001). The virtual group, either before or after education, illustrated a higher mean knowledge score. In both virtual groups and traditional education, education had a significant effect on the knowledge (P<0.001). The incremental changes in the traditional group (27.1 ± 48.1) were slightly more than in the virtual group (19.1 ± 18.1), but this difference was not statistically significant (P=0.168). However, a significant difference was seen in the percentage of learning score changes in the traditional

method compared to the virtual group (P=0.041) (Table1).

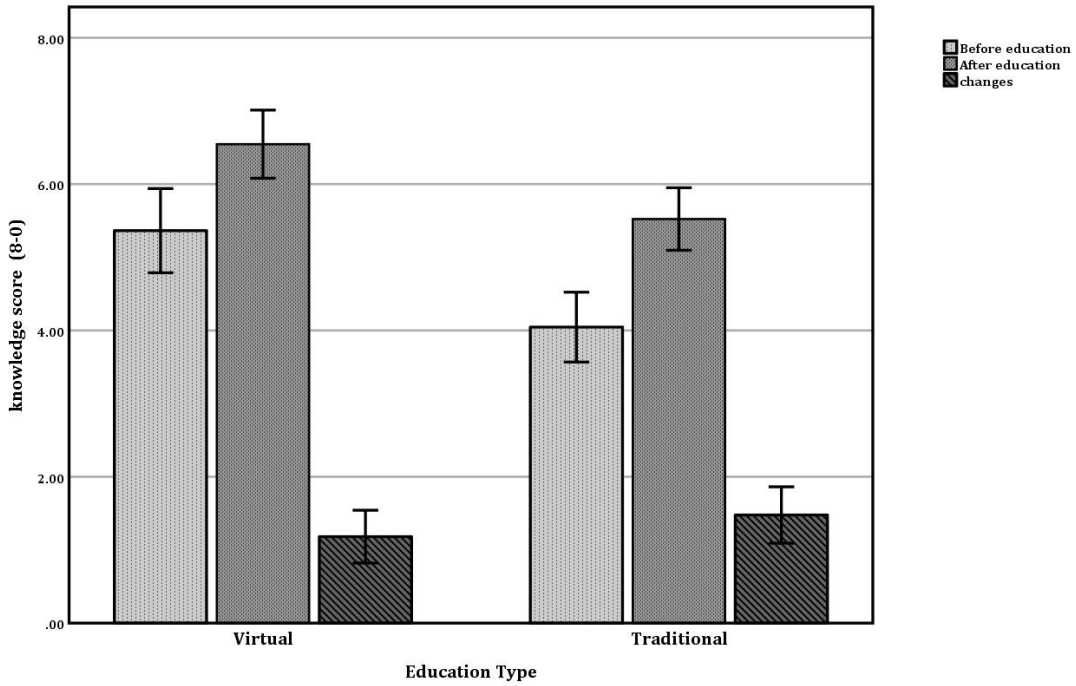


**Figure 1.** Comparing the average knowledge score before and after three days of education, and its changes in virtual and traditional methods.

**Table 1.** Comparison of knowledge score before and three days after education and its changes in the two studied groups.

| | | Education Type | | | |
|---|---|---|---|---|---|
| | | **Virtual** | **Traditional** | **Total** | **P value** |
| **Score before education** | **Mean±SD** | 5.36±189 | 4.05±1.57 | 4.70±1.85 | 0.001* |
| | **Median** | 5.50 | 4.00 | 5.00 | |
| | **Percentile 25** | 4.00 | 3.00 | 3.00 | |
| | **Percentile 75** | 7.00 | 5.00 | 6.00 | |
| **Score three days after education** | **Mean±SD** | 6.55±1.53 | 5.52±1.41 | 6.03±1.55 | <0.001* |
| | **Median** | 7.00 | 5.00 | 6.00 | |
| | **Percentile 25** | 6.00 | 5.00 | 5.00 | |
| | **Percentile 75** | 8.00 | 6.00 | 7.00 | |
| **P value** | | <0.001** | <0.001** | <0.001** | |
| **Scores changes** | **Mean±SD** | 1.18±1.19 | 1.48±1.27 | 1.33±1.23 | 0.168 |
| | **Median** | 1.00 | 2.00 | 1.00 | |
| | **Percentile 25** | 0.00 | 1.00 | 0.50 | |
| | **Percentile 75** | 2.00 | 2.00 | 2.00 | |
| **Percentage of Score** | **Mean±SD** | 37.57±78.69 | 54.30±72.36 | 45.93±75.62 | |

| | | | | | |
|---|---|---|---|---|---|
| **Changes** | **Median** | 20.00 | 40.00 | 25.00 | |
| | **Percentile 25** | 0.00 | 18.45 | 7.14 | 0.041* |
| | **Percentile 75** | 40.00 | 66.67 | 60.00 | |

SD: standard deviation, *: significant with Mann Whitney U Test, ** significant with Wilcoxon Test.

The frequency distribution of knowledge status before and after education between two groups was statistically significant, P<0.001 and P<0.004, respectively. The virtual group had a better score before and three days after the education than the other group. In general, in both groups, the knowledge status has had significant positive changes, so that in the virtual group, the percentage of good status has increased from 34.1% to 54.5%; this increase was in the traditional group from 6.8% to 22.7% (P<0.001). In addition, 82% of students had good clinical skills, and this percentage did not represent a statistically significant difference between the two study groups (P<0.999) (Table2).

**Table 2.** Comparison of knowledge score before and three days after education and its changes in the two studied groups.

| | | Education Type | | | |
|---|---|---|---|---|---|
| | | **Virtual** Score(SD) | **Traditional** Score(SD) | **Total** Score(SD) | **P value** |
| **Status of knowledge before education** | **Weak** | 7(15.9%) | 19(43.2%) | 26(29.5%) | <0.001* |
| | **Average** | 22(50%) | 22(50%) | 44(50%) | |
| | **Good** | 15(34.1%) | 3(6.8%) | 18(20.5%) | |
| | **Mean Rank** | 53.5 | 35.5 | - | |
| **Status of knowledge after education** | **Weak** | 2(4.5%) | 3(6.8%) | 5(5.7%) | 0.004* |
| | **Average** | 18(40.9%) | 31(70.5%) | 49(55.7%) | |
| | **Good** | 24(54.5%) | 10(22.7%) | 34(38.6%) | |
| | **Mean Rank** | 51.41 | 37.59 | - | |
| **P value** | | <0.001** | <0.001** | <0.001** | |

SD: standard deviation, *: significant with Mann Whitney U Test, ** significant with Wilcoxon Test.

According to the results of this study, 81.8% of the students of the virtual and traditional group had good clinical skills and there was no statistically significant difference in the two groups(P=0.999). The results showed the difference in the before-education scores of the students in the two groups was statistically significant, to prevent the effect of this score on the research results, the covariance analysis was used to measure the effectiveness of the education methods by adjusting the effects of the gender, the before education score and the GPA. The results of covariance analysis showed that after controlling the covariate variables (before education score, GPA, and gender), that did not affect the educational groups (p=/119, β=0.373, Partial Eta Squared = 0.029) (Table3).

**Table 3.** Results of analysis of covariance the effect of educational methods on learning after adjusting for the effects of previous grade, GPA and student gender.

| Parameter | B | Standard error | Sig. | 95% Confidence Interval | | Partial Eta Squared | Observed Power [b] |
|---|---|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound | | |
| Intercept | -0.076 | 1.374 | 0.956 | -2.808 | 2.657 | 0.000 | 0.050 |
| [Group=1.00] | 0.373 | 0.273 | 0.119 | -0.098 | 0.844 | 0.029 | 0.343 |
| [Group=2.00] | 0 [a] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| [Group=1.00] | -0.181 | -0.217 | 0.406 | -0.612 | 0.250 | 0.008 | 0.131 |
| [Group=2.00] | 0 [a] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Learning score-0 | 0.512 | 0.074 | 0.000 | 0.365 | 0.658 | 0.368 | 1.000 |
| GPA | 0.234 | 0.097 | 0.019 | 0.040 | 0.428 | 0.065 | 0.660 |

a: This parameter is set to zero because it is redundant, b: Computed using alpha = 0.005.

The students' GPA had statistically significant effects on their score after education (P=0.019, β =0.234) with the effect Partial Eta Squared of 0.065 (based on the division of the effective coefficient of Partial Eta Squared, the values coefficient greater than 0.14 is remarkable). The percentage of knowledge score changes in male students had a statistically significant difference between the virtual and traditional methods. Men of the traditional group had a higher percentage change, 55%compared to 17% (P=0.026). This percentage was not statistically significant in females, 33% compared to 20% (P= 0.391). There were not statistically significant differences between the two genders by type of education and GPA (Table 4).

**Table 4.** Comparison of the percentage of knowledge score changes in the two studied groups in terms of GPA and student gender.

| | | | | Education Type | | | |
|---|---|---|---|---|---|---|---|
| | | | | Virtual | Traditional | Total | P value |
| GPA | ≤15 | Percentage of scores changes | Mean±SD | 52.63±10.8.25 | 77.46±95.24 | 64.76±101.67 | 0.097* |
| | | | Median | 20.00 | 50.00 | 25.00 | |
| | | | Percentile 25 | 14.29 | 20.00 | 14.29 | |
| | | | Percentile 75 | 50.00 | 100.00 | 66.67 | |
| | 15< | Percentage of scores changes | Mean±SD | 22.52±22.00 | 33.15±31.75 | 27.95±27.64 | 0.209 |
| | | | Median | 18.33 | 33.33 | 33.33 | |
| | | | Percentile 25 | 0.00 | 0.00 | 0.00 | |
| | | | Percentile 75 | 40.00 | 60.00 | 40.00 | |
| | P value | | | 0.0595** | 0.130 | 0.171 | |
| Gender | Male | Percentage of scores changes | Mean±SD | 41.93±110.43 | 49.07±39.02 | 45.31±83.21 | 0.026* |
| | | | Median | 17.14 | 55.00 | 29.17 | |
| | | | Percentile 25 | 0.00 | 25.00 | 0.00 | |
| | | | Percentile 75 | 36.67 | 66.67 | 66.67 | |
| | Female | Percentage of scores changes | Mean±SD | 33.94±38.36 | 57.91±89.09 | 46.41±69.91 | 0.391 |
| | | | Median | 20.00 | 33.33 | 25.00 | |
| | | | Percentile 25 | 14.29 | 14.29 | 14.29 | |
| | | | Percentile 75 | 45.00 | 66.67 | 50.00 | |
| | P value | | | 0.393 | 0.421 | 0.946 | |

SD: standard deviation, *: significant with Mann Whitney U Test, ** significant with Wilcoxon Test.

## Discussion

The last few decades have seen a shift from traditional medical education to online education, virtual networks or e-learning (19). Distance or online education has been used as an important educational feature in different countries in the past years (20,21) and according to statistics, almost 30% of students of USA have used distance education courses during their bachelor's degree (22), but in reality this type of

education in medical education not widely used in some country.

In this study, the experiences of clinical medical students in e-learning were conducted through social media training via WhatsApp application, which is a new approach to teaching in the medical school of Guilan University of Medical Sciences during the COVID-19 pandemic. According to the results, the post test scores of medical students have increased significantly in both groups. It seems that education alone is effective at the level of knowledge of clinical medical students. Of note, the knowledge's score of clinical medical students who participated in virtual groups was higher than those who received a traditional education (face to face). In the current study, it was shown that changes in knowledge scores in male students were more in the virtual group compared to the traditional one.

Contrary to our study, researchers showed that the score of using the first principle of education in the traditional educational group was increased significantly from the virtual educational group (23). Of note, learning is a personal characteristic, and people have own progress in learning according to their abilities, so it seems that there is a difference in the score of the first principle of education in e-learning and traditional education group. Koenigs et al., stated that students' attitudes toward the learning environment affect behaviors and the quality of learning outcomes (24). Also, other researchers found that if the first principle of education is used in e-learning, that could motivate learners (25). Other study showed that e-learning could facilitate the learning process (26). According to similar studies the result of present study suggested the blended method as the most effective one to improve learning quality (27).

Researchers represented that the traditional teaching method is reliable for achieving educational goals. The new generation of medical students have access to high standards and valuable digital resources. New teaching methods and e-learning alone are not a solution for teaching skills. So, the traditional learning method mixed with e-learning may help student learning process (28) and the digital valuable resources can be well used as a combined learning strategy. Because virtual education has provided a new environment for learning and reduces traditional educational limitations such as time and place limitations (29). Therefore, the virtual training method might be useful for people who do not have enough time for face-to-face training.

Indeed, Wu et al. results showed a significant difference in the score of students in the theoretical courses. The results of their study indicate that the kind of virtual education, the use of interactive animations due to the activities involving students in education have a better impact on the understanding of the scientific content, and promote their knowledge (30). Other researchers suggested that e-learning environments may use as part of blended learning and improve of clinical skills quality (31). In contrast to our results, some studies revealed that there was no significant difference in the mean of total scores before education between the virtual and traditional groups (32). It is expected that virtual education can partially replace the traditional method of providing theoretical knowledge but not clinical knowledge and skills (33). In this era, there is a great emphasis on life time learning and effective education. Social networks and E-learning resources in medical education facilitate the learning process for medical professionals, so the effective use of these technologies in medical education might help achieve valuable results (34,35). The availability, the independency of time, and the place of e-learning have led to its widespread use by students. It noted that the pervasiveness of e-learning requires contexts and infrastructures, the preparation of which requires time, money, and extra planning (35).

## Conclusions

According to the results of this study, the average and mean score of knowledge in the medical students who participated in WhatsApp groups was significantly higher than others who had received traditional training. It seems that the virtual education method in combination with the traditional may improve the learning process in medical students. It seems that e-learning has a significant role in learning theoretical courses in the future, but it may not be an entire replacement for practical and face-to-face learning. So, it suggests that a combined approach (traditional and e-learning) will be the most appropriate method for future medical education.

## Author contribution

**SMZZ** conceptualization, writing - review & editing, **ZR** assistant researcher, **MF** writing - review & editing, **NNR** methodologist/assistant researcher, **AK** data curation, writing - original draft, **RTK** assistant researcher, **EKL** methodologist, assistant researcher. All authors confirmed the final version of the paper.

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## Conflict of interest

There are no potential conflicts of interest.

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# Seroprevalence of strongyloides stercoralis among cancer patients in an endemic region in Iran

Fatemeh Nejatifar [1], Sheida Dejabad [2], Maryam Shakiba [3], Sirous Gharib[1], Afshin Shafaghi [4]*

[1] Department of Hematology and Oncology, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2] Department of Internal Medicine, Razi Hospital, Guilan University of Medical Sciences, Rasht, Iran

[3] Cardiovascular Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran

[4] GI Cancer Screening and Prevention Research Center (GCSPRC), Guilan University of Medical Sciences, Rasht, Iran

## Abstract

**Introduction:** Strongyloides stercoralis a globally widespread human intestinal nematode. Hyperinfection mainly appears in patients with defective immune systems . This study intended to investigate the prevalence of serum positive Strongyloides stercoralis in cancer patients who have never undergone chemotherapy and those who received at least one cycle of chemotherapy.

**Materials and Methods:** This study targeted cancer patients, referred to Rasht hospital, and assigned them to two groups of cancer patients with no history of chemotherapy and cancer patients with at least one cycle of chemotherapy. Patient's demographic information, underlying diseases and chemotherapy regimen were recorded, and their serum sample was examined.

**Results:** 410 patients were included in this study. the majority were female ( 51/7% ). About 40 patients tested positive for serology, out of which 14 were in the chemotherapy-treated group and 26 in chemotherapy-untreated group, indicating that the prevalence of serum positive Strongyloides stercoralis was significantly higher in patients with no history of chemotherapy. Moreover, eosinophilia significantly correlated with the prevalence of seropositivity. The chemotherapy protocol containing high doses of corticosteroids could multiply the risk of positive serology by 12.7 times.

**Conclusion:** Before chemotherapy, in areas with a higher prevalence of Strongyloides stercoralis, especially in high corticosteroids protocols, it may make sense to study Strongyloides stercoralis . It becomes more vital in men and eosinophilic patients. Since serologic testing may display false negative rates in patients with defective immune systems, subsequently, alternative complementary methods such as fecal larval examination and fecal PCR test are highly suggested to be carried out along with serology.

**Keywords:** Strongyloides stercoralis, Serology, Cancer, Chemotherapy

*Corresponding Author: Afshin Shafaghi

✉ Email: drafshinshafaghi@gmail.com

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## Introduction

Strongyloides stercoralis is a globally widespread human intestinal nematode that can be easily transmitted esp. in regions with low sanitation conditions. This nematode has an autoinfection cycle in human hosts where it can have a lifelong stay if remained untreated (1-4). Infection of humans with this nematode occurs through the third stage larvae or filariasis that can be through the skin or the mouth feces. The adult female worm lives in the small intestine and is asymptomatic in most people (5, 6). Strongyloides stercoralis mainly appears as gastrointestinal, respiratory (Löffler's syndrome) and peripheral eosinophilic symptoms. Gastrointestinal symptoms of this parasite include nausea, diarrhea and vomiting (7-9). Patients with defective immune systems, AIDS, and malnutrition as well as organ transplant recipients and corticosteroid-treated ones are more prone to the risk of Hyperinfection that will lead to death if left untreated (10-12). An estimated %87 of worldwide deaths are caused by Hyperinfection. Filiform larvae migrate to the heart, liver and central nervous system, resulting in their inflammation and dysfunction in patients with defective immune systems (13, 14). Strongyloides stercoralis is mainly diagnosed through microscopic examination of fecal samples; since this diagnostic method has less sensitivity, many cases remained undiagnosed (15). There are various antigen-based diagnostic methods for testing Strongyloides stercoralis nematode. High sensitivity methods used for diagnosing this nematode involve the use of immunoglobulin isotypes and PCR-based tests for detecting Strongyloides stercoralis-derived DNA in feces (16-18). The sensitivity of ELISA assay technique is about %88-94, having false-negative results in hosts with defective immune systems. Positive rates may appear in the presence of other worm-induced infections. As Strongyloides stercoralis is highly frequent in the northern region of Iran, the present study intended to investigate the prevalence of serum strongyloidiasis in cancer patients who have never undergone chemotherapy and those who received at least one cycle of chemotherapy based on serologic testing because other laboratory testing methods were not available in the intended areas.

## Materials and Methods

### Study design and study population

This was a descriptive cross-sectional study that was performed on cancer patients admitted on an outpatient basis to Razi Hospital, a referral center in Rasht, north of Iran. The statistical population consisted of two groups of patients: the first group of cancer patients who had not yet received chemotherapy and the second group of patients with cancer who had undergone at least one course of chemotherapy. Patients who have received anti-nematode medication in the past three months, HIV sero-positive, history of organ transplant, or receiving immunosuppression excluded from the study. According to the prior prevalence of Strongyloides stercoralis in chemotherapy-treated (33%) (19) and chemotherapy-untreated (10%) (20) patients, considering 5% confidence limit and 5% margin of error, 236 and 174 sample was determined for chemotherapy-treated and chemotherapy-untreated groups, respectively. This classification was aimed at enabling determination of strongyloidiasis prevalence in patients with and without chemotherapy. The study protocol was approved by the Institutional Review Board of Guilan University of Medical Sciences. Patients were first informed about the purpose of the study and they were taken informed consent to participate in the study.

### Data collection

Patient’s demographic information, including age, sex, place of residence, underlying diseases, chemotherapy regimen, current smoking and alcohol consumption were recorded, and their serum sample was collected and examined using serologic tests. ELISA assay was used to detect IgG (Nova Tec Immundiagnostica GmbH, Germany. specificity 94.12%, sensitivity89.47%) . Eosinophilia was defined as an absolute eosinophil count ≥ 500 /microl in peripheral blood.

### Statistical analyses

Patients' characteristics and IgG seropositivity were described using frequency and percent. A Chi-square test was applied to detect the association between patients' characteristics and IgG seropositivity. Multivariate logistic regression was used to estimate

adjusted odds ratio (OR) for predictors of seropositivity with 95% confidence interval (CI). A P-value less than 0.05 was considered significant. Data were analyzed using Stata 14.

## Results

Out of 410 patients who participated in this study, 212 (%51.7) were female and the highest number of patients (51.5%) were in the age group of 40-60 years. The mean age of participants was 53.27±14.08 years, with the youngest patients aged 17 and oldest 90 years. Table 1 presented demographic information of the patients.

Of the total, 40 patients (%9.8) were positive for IgG serology, out of which 14 (%5.9) were in chemotherapy-treated group and 26 (%14.9) in chemotherapy-untreated group, indicating that the prevalence of serum strongyloidiasis was significantly higher in patients with no history of chemotherapy than chemotherapy-treated ones (P-value: <0.002).

According to the results, there was a significant relationship between sex of patients and the prevalence of serum strongyloidiasis, meaning that serum strongyloidiasis was significantly higher in male than female subjects (P=0.004).

However, other characteristics including place of residence, type of cancer, smoking status, alcohol abuse, underlying diseases, metastasis and chemotherapy sessions, did not significantly correlate with the prevalence of serum strongyloidiasis.

Out of 41 eosinophilic patients, 28 (%68.3) were positive for serology, amongst which 10 (%66.7) were in chemotherapy-treated group and 18 (%69.2) were in chemotherapy-untreated group. Accordingly, there was a significant relationship between eosinophilia and the prevalence of serum strongyloidiasis in cancer patients (P<0.001).

**Table 1.** prevalence of IgG seropositivity according to the patient's characteristics in Razi medical education center in Rasht.

| Variable | | Frequency | IgG seropoitivity | |
|---|---|---|---|---|
| | | | N | % |
| **Sex** | Male | 198 | 28 | 14.1 |
| | Female | 212 | 12 | 5.7 |
| **Age Range** | <40 years | 74 | 5 | 6.8 |
| | 40-60 years | 211 | 18 | 8.5 |
| | >60 years | 125 | 17 | 13.6 |
| **Occupation** | Housewife | 123 | 9 | 7.3 |
| | Official clerk and Worker | 198 | 20 | 10.1 |
| | Farmer | 41 | 8 | 19.5 |
| | Unemployed | 48 | 3 | 6.2 |
| **Place of Residence** | City | 258 | 26 | 10.1 |
| | Village | 80 | 7 | 8.8 |
| | Urban suburbs | 72 | 7 | 9.7 |
| **Sessions of Chemotherapy*** | 1-5 sessions | 127 | 5 | 3.9 |
| | > 5 sessions | 109 | 9 | 8.3 |
| **Eosinophilia** | Positive | 41 | 28 | 68.3 |
| | Negative | 369 | 12 | 3.3 |
| **Corticosteroid-containing regimen*** | Yes | 22 | 4 | 18.2 |
| | No | 214 | 10 | 4.7 |
| **Current Smoking** | Yes | 106 | 12 | 11.3 |
| | No | 304 | 28 | 9.2 |
| **Alcohol consumption** | Yes | 34 | 4 | 11.8 |
| | No | 376 | 36 | 9.6 |

* These variables were measured in chemotherapy-treated group

Statistical results showed that 22 of 236 chemotherapy-treated patients had high-dose corticosteroid-containing regimens, 4 of whom (%18.2) tested serologically positive. In other words, there was a significant relationship between the type of chemotherapy regimens and the prevalence of serum strongyloidiasis in patients treated with chemotherapy (P=0.031).

Multivariate logistic regression model status showed that male patients (OR=3.43, 95% CI:1.32-8.89) and eosinophilia (OR=70.6, 95% CI:27.8-178.8) were independent predictors of IgG seropositivity. The sub-group analysis in chemotherapy-treated group revealed that corticosteroid-containing regimen and eosinophilia were independently associated with increased odds of IgG seropositivity.

## Discussion

Strongyloidiasis is a parasitic infection with widespread distribution in regions with a humid climate like the north of Iran. It is associated with the risk of death in people with an immunosuppressive system .

According to the results of this study, serum positive Strongyloides stercoralis was more prevalent in cancer patients by 9.8 percent (5.9-14.9). Baiomy et al. (2010) found an approximated %6.3 frequency of serum strongyloidiasis in Egypt (21). As reported by Rafiei et al. (2016), Ahvaz showed %14.4 prevalence of the disease (20). In preceding Iranian studies, strongyloidiasis was more widespread in northern regions of Iran such as Guilan due to their humid climate. Sajjadi et al. (2002) showed that the prevalence of strongyloidiasis was %6.1 (22). As this study indicated, the risk of positive serology was significantly higher in chemotherapy-untreated than chemotherapy-treated patients; the reason may contribute to the false negative results of serologic tests, generation of various antibody subtypes and failure to find antibodies in acute phase of the disease. The presence of other parasites such as schistosomiasis, ascaris, etc. may associate with positive serology. Mendez et al. (2016) revealed that false negative serologic test results were allied to a defective immune system, with higher rates in chemotherapy-treated than chemotherapy-untreated patients. Other causes of false negatives depend on the emergence of various antibody subtypes, except for IgG, as well as the lack of antibodies in acute phase of the disease (23). In a fecal examination, Azizi et al. (2012) showed that intestinal parasites were prevalent in the group of chemotherapy-treated patients by %24.8 and in chemotherapy-untreated group by %28 (24). Similarly, the observed frequency was higher in patients untreated with chemotherapy than those treated with chemotherapy in this study; that is because of the effect of chemotherapy drugs on parasite growth control and exposure for patients in critical care unit .

Eosinophilia increased the risk of positive serology by 70, which was in line with Ashrafi's et al. (2008) study in Guilan (25). Lotfi et al. (2002) reported eosinophilia in about %83 of patients with strongyloidiasis (26).

According to Mendez et al. (2016), eosinophilia was more frequently witnessed in patients with strongyloidiasis (23).

Corticosteroids can suppress the immune system at certain doses and provide the ground for the risk of different parasitic and bacterial infections. The results of this study were representative of statistical relationship between corticosteroid-containing chemotherapy regimen and the prevalence of serum strongyloidiasis, implying that corticosteroid can increase the risk of positive strongyloidiasis serology by 12.7 times in chemotherapy-treated patients. Fardet et al. (2007) stated that strongyloidiasis should be considered a potential risk in all corticosteroid recipients (27). Corti et al. (2016) found that strongyloidiasis appeared as Hyperinfection in immunosuppressive patients esp. recipients of high-dose corticosteroid in Argentina (28). According to Keiser's et al. (2004) study in Maryland, immunosuppression is associated with Hyperinfection in strongyloidiasis with the significant effect of corticosteroid (29). Mendez et al. (2016) found that corticosteroid is the most common risk factor for strongyloidiasis progress even in its short-term use (23).

Furthermore, the findings of this study displayed that male patients were 3.6 times more prone to the risk of positive serology. In their study, Sharif Dini et al. (2018) showed that infection was more prevalent in

men due to their frequent exposure to infectious sources in outdoor activities and open-air jobs (30). Another main category in cancer investigations besides genetics and also clinical investigations is the fluctuation of DNA methylation. Meaningly, DNA methylation is one of the most important parts of epigenetics that always has a notable impression on carcinogenesis and tumorigenesis. Consequently, it is recommended that selecting some important genes and also the investigating of their epigenetics (DNA methylation) can lead to a notable result (31-35).

In finale, there was no significant relationship between the prevalence of serum positive strongyloidiasis and patients' age, occupation, type of cancer, metastasis, chemotherapy sessions, smoking status, alcohol abuse and place of residence in this study.

## Conclusions

Regarding the risk of exacerbation of the disease and the spread of widespread disease in immunocompromised individuals, it is recommended that people with cancer who are scheduled to receive a corticosteroid regimen be screened for chemotherapy before chemotherapy to prevent the disease from progressing. It is more important in men with eosinophilia. Since the prevalence of strongyloidiasis appeared to be lower in chemotherapy-treated patients than chemotherapy-untreated ones, serologic testing method per se seems to be not sufficient; subsequently, further studies with larger sample size and fecal PCR-DNA comparisons are suggested to be carried out along with serology testing. Moreover, as testing results may display false negative rates in chemotherapy-treated patients, endemic regions should be serologically tested for the disease before initiating chemotherapy.

### Author contribution

**FN** is hematologist and medical oncologist managed the patients and participated in the drafted manuscript. **ASh** is gasterentrologist managed the patients and participated in the drafted manuscript. **MSh** performed statistical analysis. **SGh** collected data and manage the patients. **ShD** collected data and participated in the drafted manuscript. All the authors read and approved the final manuscript**.**

### Ethical approval

This study was approved by the ethic committee of guilan university of medical sciences with ethics code of IR.GUMS.REC.1398.110.

### Conflict of interest

No potential conflict of interest was reported by the authors.

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# Evaluation of demographic status and related factors in mortality of patients suspected of COVID-19 admitted to Razi Hospital in Rasht

Morteza Rahbar Taramsari [1]*, Ali Monfared [2], Alireza Badsar [1], Hamid Mohammadi Kojidi [1], Shima Ildari [3], Jalal Kheirkhah [4], Saeed Najjar Soltani [3]*, Fatemeh Saberhamishegi [3], Erfan Bozorgzade Ahmadi [3], Habib Eslami Kenarsari [5]

[1] Department of Forensic Medicine, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2] Urology Research Center, Razi Hospital, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[3] Inflammatory Lung Diseases Research Center, Guilan University of Medical Sciences. Rasht, Iran

[4] Department of Cardiology, Healthy Heart Research Center, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[5] Clinical Research Development Unit of Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran

## Abstract

**Introduction:** SARS-CoV2 is the third strain from Corona family with zoonotic roots which has spread among humans from the beginning of this century. We conducted this study to examine mortality and its related factors among all patients admitted to Razi Hospital with suspicion of COVID-19 between February and April 2020.

**Materials and Methods:** In this analytical cross-sectional study,after obtaining permission from the ethics committee under the university's research deputy, the required information such as demographic data, clinical symptoms and imaging study results was collected by reviewing records of all patients with COVID-19 suspicion.

**Results:** From 1792 cases, 1045 patients were male and 747 patients were female. Mortality was 27% in all patients and 30% and 22% in men and women. The highest hospitalization rate was in the age group of 51-60 years and the highest mortality rate was in the age group of 81-90 years. 1472 patients lived in urban areas and 316 patients in rural areas. 997 patients had 93% O2 Saturation and less, of which 36% died. PCR test was performed for 505 patients, of which 69% were positive. Chest CT scan was performed in 96% of patients and chest X-ray was performed in 66% of patients with COVID-19.The most common symptoms were shortness of breath, cough, fever, chills, weakness, nausea and headache, respectively. The highest mortality was in patients with impaired consciousness at the beginning of hospitalization.

**Conclusion:** The results of the present study showed that male gender, older age, history of underlying disease, Chest x-ray involvement, drug use, shortness of breath and lesser O2 Saturation are associated with adverse outcomes, constitutional and gastrointestinal symptoms are associated with better outcomes in patients with COVID-19.

**Keywords:** Coronavirus, Acute respiratory syndrome, SARS-CoV-2, COVID-19, Mortality

**Corresponding Authors:** Morteza Rahbar Taramsari ✉ Email: rahbar_m46@yahoo.com

Saeed Najjar Soltani ✉ Email: saeed_najjarsoltani@yahoo.com

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## Introduction

Coronaviruses are a type of Coronaviridae. Coronaviridae is a family of enveloped, sensitive, positive, single-stranded RNA viruses that has the largest viral genome (26-33 kb) among RNA-infected viruses. The family Coronaviridae consists of two subfamilies called "Coronavirinae" (Coronavirus) and "Torovirinae" (Torovirus). Coronavirus can be divided into four groups based on phylogenetic classification: "Alpha, Beta, Gamma and Delta" (1). Few studies are showing that bats can host many types of coronaviruses, which varies depending on the habitat and the type of bat (2).

In general, coronaviruses cause a mild respiratory illness in humans with cold-like symptoms; But the ability to cause severe and even fatal respiratory diseases has been proven (3). A type of coronavirus called "Coronavirus 2019" was identified on December 31, 2019, in Wuhan, China, also known as "COVID-19". According to the analyzes, the amino acid positions of 501, 723 and 1010 have changed with the SARS virus, a stable mutation in non-structural protein 2 (nsp2) has resulted in COVID-19 being more contagious than in SARS. Also, the nsp3 destabilizing mutation caused an acceptable difference between SARS and COVID-19 (4). In a 2020 study by Huang C et al. to evaluate clinical findings in patients with coronary artery disease, laboratory features included leukopenia (25%), lymphopenia (25%), and increased aspartate aminotransferase (Seven of the 28 patients are non-ICU( 37%)). In ICU patients, prothrombin and D-dimer levels were increased in admission compared to non-ICU patients. Elevated troponin (troponin-sensitive I (HS-cTnI)) was detected in five patients, possibly indicating virus-associated myocardial damage. Abnormalities in computed tomography (CT) of the chest were observed in all patients. Ninety-eight percent had a two-way conflict, and grand glass turbidity was generally seen. Complications included acute respiratory syndrome (29%) and secondary infection (10%) (5). In a 2020 study, Salehi et al. performed imaging findings in patients with coronary artery disease. One of the known features of COVID-19 in primary CT is multilobar ground-glass (GGO) opacity with peripheral or posterior distribution, mainly in the lower lobes and less in the right middle lobe. Abnormal early imaging findings of GGO opacities may be seen in a smaller number of cases, mainly in the elderly. Septal thickening, bronchiectasis, pleural thickening, and subpleural involvement are some of the less common findings, which are mainly seen in later stages of the disease. Pleural effusions, pericardial effusions, lymphadenopathy, cavitation, halo symptoms, and pneumothorax are very rare but may be seen as the disease progresses (6). Follow-up of CT in the next stage of the disease, with an increase in the number and size of GGOs and gradual conversion of GGO to multifocal turbidity, thickening of the septum and the formation of a paving pattern, is seen most strongly in CT findings on day 10 after the onset of symptoms. The acute respiratory syndrome is the most common symptom for the transfer of patients with COVID-19 to the ICU and the leading cause of death in this patient population. Imaging patterns of clinical improvement usually occur after 2 weeks of illness and include the gradual removal of opacities and a reduction in the number of lesions and lobes involved (6). Since various factors from age, gender and place of residence, to underlying diseases and special medical conditions from common cases such as diabetes to special cases such as cancer treatment or organ transplantation, along with the patient's symptoms are known to be effective in disease severity and outcome. In this study, the mortality rate of patients suspected of having COVID-19 was admitted in February and April 2020 and their relationship was examined based on statistical analysis.

## Materials and Methods

### Study population

In this cross-sectional-analytical study, after obtaining permission from the Ethics Committee in University Research at Guilan University of Medical Sciences (IR.GUMS.REC.1399.245), the data of all hospitalized patients suspected of having COVID-19 based on positive signs in favor of Corona, CT scan report and simple chest X-ray report in Razi Hospital in Rasht during February and April 2020 were reviewed.

### Statistical analyses

After collecting the data, the data were entered into SPSS software version 22 and to describe them, relevant and appropriate statistical tables and graphs

were extracted. Chi-square and Fisher tests were used to investigate the possible relationship between the variables and the outcome of patients' deaths.

## Results

In order to conduct the study, 1796 files were studied and 4 files were excluded due to lack of information. According to Table 1, out of 1792 patients, 484 (27%) died and 1308 (72.9%) recovered. There were 1045 male and 747 female patients, which accounted for 58.3% and 41.6% of the population of COVID-19 patients admitted during February and April 2020, respectively. 315 patients (30.1%) died among men and 169 patients (22.6%) among women. This rate is 17.5% for dead men compared to the total number of patients studied and for women 9.4%. There was a statistically significant relationship between being a man and mortality rate (P <0.001); Male patients were more likely to die than female patients.

**Table 1.** Frequency distribution of gender of patients in terms of outcome.

| Gender | | Consequences | | Total | P-value |
|---|---|---|---|---|---|
| | | Recovery | Death | | |
| Male | Number | 730 | 315 | 1045 | <0.001 |
| | Percent | 69.8 % | 30.1% | 100.0 % | |
| | Percent of total | 40.7 % | 17.5% | 58.3% | |
| Female | Number | 578 | 169 | 747 | |
| | Percent | 77.3 % | 22.6% | 100.0 % | |
| | Percent of total | 32.2 % | 9.4% | 41.6% | |
| Total | Number | 1308 | 484 | 1792 | |
| | Percent | 72.9 % | 27.0% | 100.0 % | |

82.3% (1472 people) of patients admitted to the city and 17.7% (316 people) lived in the village. The mortality of patients living in urban areas was 25.5% (375 cases) and 33.5% (106 cases) among villagers. Rural residents were higher than urban residents (33.5% vs. 25.5%).

The age of the patients in the study was between 16 and 100 years with a mean of 58.8 ± 15.7. The mortality rate of patients over 58.5 years was 37.8% and in the group less than 58.5 years was 15.5%. There was a statistically significant relationship between age over 58.5 years and death rate (P <0.001); This means that patients aged 59 years and older died more than those aged 59 years (37.8% vs. 15.5%).

8 patients (0.4%) in the age group of 16-20 years (100% recovery), 61 patients (3%) in the age group of 21-30 years (90% recovery, 9% death), 183 People (10%) in the age group of 31-40 years (90% recovery, 9% death), 308 people (17%) in the age group 41-50 years (82% recovery, 7% death), 396 people (22% ) In the age group 51-60 years (78% recovery, 21% death), 385 people (21%) in the age group 61-70 years (67% recovery, 32% death), 273 people (15%) in the age group -71 80 years (59% recovery, 40% death), 158 people (8%) in the age group 81-90 years (53% recovery, 46% death), 20 people (1%) in the age group 91-100 years (55% recovery) , 45% feet). The highest hospitalization rates for both men and women were in the age group of 51 to 60 years with 12% and 9%, respectively. The highest mortality rate of men, as well as all patients regardless of gender, was in the age group of 81 to 90 years (46%) and for women in the age group of 91 to 100 years (55%).

The mean length of hospital stay of the studied patients was 5.4 days with a standard deviation of 4.7 days. Considering the cut-off of 5.5 days; 1147 patients have been hospitalized less than this period, with a death rate of 28.7% (329 cases) (68.8% of all deaths) in this group and 23.4% (149 cases) (31.2% of total deaths) among patients who have been hospitalized for more than this period. Deaths). There was a statistically significant relationship between the length of hospital stay and death rate (P = 0.016) so that in patients with a length of hospital stay of 5 days and less than patients admitted more than 5 days more death rate occurred (28.7% vs. 23.4 %).

Based on the information in Figure 1; 9.1% of patients were smokers, 3.9% were opium users, and 0.9% of patients admitted reported smoking and opium at the same time. In these three groups, the mortality rate was 25.5%, 45.6% and 46.7%, respectively. The mortality of people who had no history of smoking or opium (1484 people) was 25.9%. There was a statistically significant relationship between opium use (with or without smoking) and mortality (P = 0.002); Patients with a history of opium addiction (with or without

smoking) had a higher mortality rate than those without a history of addiction.

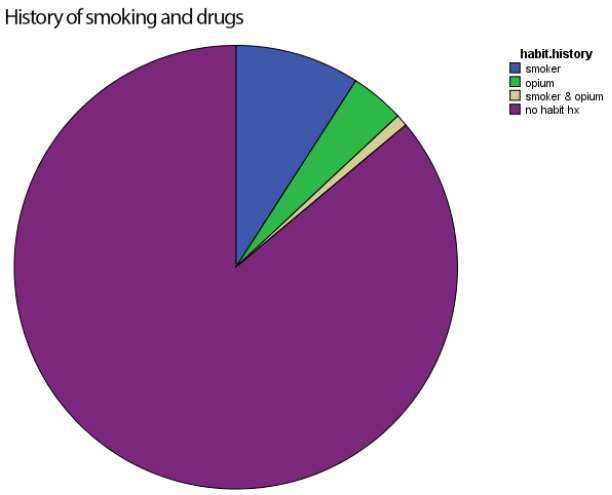


**Figure 1.** Frequency of patients by the history of smoking and opium.

Based on the information; 64.6% of hospitalized patients reported a positive history of underlying diseases. The mortality rate in this group was 32.7%, while among patients with no history of the underlying disease (35.4% of patients), 16.5% died and 83% recovered and were discharged. The number of people who had no underlying disease or previous medical history and died made up 5.9% of the total study population and the remaining 21.1% of the population who died had a history of the underlying disease. There was a statistically significant relationship between having a history of one of the underlying diseases and mortality (P <0.001); So that in any of the underlying diseases, the mortality rate was higher than people without a history of any disease.

Of all the cases, 151 were hospitalized in the intensive care unit, of which 131 (86%) died and 20 recovered. Of these, 115 (76.2%) had a history of the underlying disease. 93 people (61%) were men. There was a statistically significant relationship (P <0.001) between hospitalization in the intensive care unit and death outcome. There was also a statistically significant relationship (P <0.001) between male gender and history of the underlying disease with hospitalization in intensive care unit; So that male patients either with a history of underlying disease were admitted to the intensive care unit more than female patients or without a history of the underlying disease, and also among patients admitted to the intensive care unit more death rate than Occurred patients admitted to the emergency department.

According to Table 2 and Figure 2; Mortality in patients with hypertension was 33.8%. It is noteworthy that 38.3% of all deaths were due to this disease and 73% of recovered people had no history of this disease. Also, the death rate among people who did not have a history of hypertension was 23.9%. Diabetes improved by 68%, compared with 75% among people without a history of diabetes (excluding other diseases). 23.4% of patients with hyperlipidemia died.

The mortality rate among hospitalized cardiovascular patients was 36.5% and 7% of the total population died with a history of this disease. A history of stroke has been associated with 40% of deaths. Also, the mortality rate in respiratory diseases was 34.3% and 12.2% of the total death population were involved in respiratory diseases.

In conditions of suppression or immune system disorders such as cancer, chemotherapy and radiotherapy, as well as the use of immunosuppressive drugs and a history of transplant mortality was higher than the total average. The highest mortality rate was among people with a history of radiotherapy (66.7%).

There was a statistically significant relationship (P <0.001) between the history of hypertension, cardiovascular disease, history of cancer and mortality. Also between diabetes (P = 0.003), liver disease (P = 0.004), history of radiotherapy (P = 0.005), history of respiratory disease (P = 0.024), neurological disease (P = 0.010) and use of suppressive drugs Immune system (P = 0.046) was also observed to have a statistically significant relationship with mortality. So that the death rate in patients with any of the above diseases was higher than patients with a negative history of that disease.

There was no statistically significant relationship between hyperlipidemia, CVA, kidney and thyroid disease and history of organ transplantation and mortality.

**Table 2.** Frequency of each case of underlying disease and death rate.

| Disease | Positive history | Death rates | P value | Disease | Positive history | Death rates | P value |
|---|---|---|---|---|---|---|---|
| **Blood pressure** | 30.4% | 33.8 % | <0.001 | **Radiotherapy** | 0.7% | 66.7% | 0.005 |
| **Diabetes** | 28.8% | 32% | 0.003 | **Chemotherapy** | 1.7% | 43.3% | 0.059 |
| **Hyperlipidemia** | 11% | 23.4% | 0.235 | **Taking immunosuppressive drugs** | 1.1% | 57.9% | 0.004 |
| **Cardiovascular disease** | 19.1% | 36.5% | <0.001 | **Liver disease** | 7.4% | 31.8% | 0.221 |
| **Respiratory problems** | 9.6% | 34.3% | 0.024 | **Kidney disease** | 3.3% | 31.7% | 0.459 |
| **Stroke** | 2.2% | 40% | 0.128 | **Thyroid problem** | 2.5% | 44.4% | 0.010 |
| **Cancer** | 3.2% | 56.1% | <0.001 | **Neurology and psychiatry** | 4.7% | 36.5% | 0.046 |
| **Organ transplantation** | 2.1% | 35.1% | 0.264 | | | | |

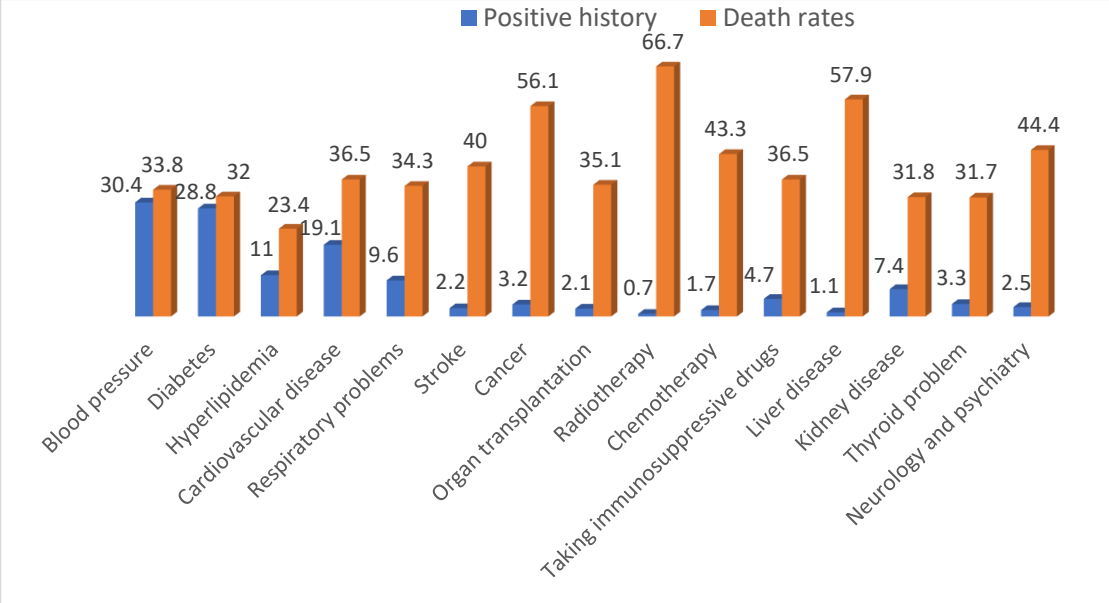


**Figure 2.** Prevalence of each underlying disease and death rate.

According to Table 3 and Figure 3; 1137 patients (64.6%) had fever and 623 patients (35.4%) did not have fever. 274 patients (24.1%) died in fever group and 193 (31.0%) deaths in non-fever group. There was a statistically significant relationship between the absence of fever and the rate of death (P = 0.002) so that in patients without fever the rate of death was higher than patients with fever (31.0% vs. 35.4%)

657 patients (37.4%) had chills and 1101 patients (62.6%) did not have chills. 139 patients (21.2%) with chills symptoms and 328 patients (29.8%) in patients without chills died. There was a statistically significant relationship between the absence of shivering and the rate of death (P <0.001) so that in patients without shivering the rate of death was higher than those with shivering (29.8% vs. 37.4%)

1239 patients (70.4%) had a cough and 520 patients (29.6%) had no cough. The death rate was 314 (25.3%) in people with cough and 153 (29.4%) in the group without cough. There was no statistically significant relationship between cough and death rate (P = 0.086).

1401 patients (79.6%) had shortness of breath and 358 patients (20.4%) had no shortness of breath. 424 patients (30.3%) died in patients with shortness of breath and 43 patients (12%) died in the group without shortness of breath. There was a statistically significant relationship between the symptoms of shortness of breath and the rate of death (P <0.001) so that the rate of death in patients with shortness of breath was higher than patients without shortness of breath (30.3% vs. 12%).

10.8% of the patients had a headache, 5.9% had diarrhea and 27.5% had myalgia. Mortality in each was 25.8%, 19.4% and 24.2%, respectively. There was no statistically significant relationship between headache, diarrhea and myalgia symptoms with death rate.

104 patients (5.9%) had decreased level of consciousness, of which 73 (70.2%) died. There was a statistically significant relationship (P <0.001) between decreased level of consciousness and mortality; The death rate was higher among patients with decreased level of consciousness than those without this symptom (70.2% vs. 23.8%).

The frequency of patients with nausea was 12.2%, vomiting 8%, weakness and lethargy 17.8%, sore throat 3.4% and neurological symptoms 0.9%. The mortality rates in each were 15.3%, 13.6%, 16.9%, 13.6%, and 17%, respectively. There was a statistically significant relationship between the absence of the above symptoms and mortality (P <0.05); So that the rate of recovery in people with these symptoms was higher than people without them.

**Table 3.** Frequency distribution of clinical symptoms in the studied patients according to the outcome.

| Clinical symptoms | | | Consequences | | Total | P value |
|---|---|---|---|---|---|---|
| | | | Recovery | Death | | |
| **Fever** | Yes | Number | 863 | 274 | 1137 | 0.002 |
| | | Percent | 75.9% | 24.1% | 64.6% | |
| | No | Number | 430 | 193 | 623 | |
| | | Percent | 69.0% | 31.0% | 35.4% | |
| **Chills** | Yes | Number | 518 | 139 | 657 | <0.001 |
| | | Percent | 78.8% | 21.2% | 37.4% | |
| | No | Number | 773 | 328 | 1101 | |
| | | Percent | 70.2% | 29.8% | 62.6% | |
| **Cough** | Yes | Number | 925 | 314 | 1239 | 0.086 |
| | | Percent | 74.7% | 25.3% | 70.4% | |
| | No | Number | 367 | 153 | 520 | |
| | | Percent | 70.6% | 29.4% | 29.6% | |
| **Shortness of breath** | Yes | Number | 977 | 424 | 1401 | <0.001 |
| | | Percent | 69.7% | 30.3% | 79.6% | |
| | No | Number | 315 | 43 | 358 | |
| | | Percent | 88.0% | 12.0% | 20.4% | |
| **Headache** | Yes | Number | 141 | 49 | 190 | |
| | | Percent | 74.2% | 25.8% | 10.8% | 0.862 |
| | No | Number | 1151 | 418 | 1569 | |
| | | Percent | 73.4% | 26.6% | 89.2% | |
| **Diarrhea** | Yes | Number | 83 | 20 | 103 | 0.107 |
| | | Percent | 80.6% | 19.4% | 5.9% | |
| | No | Number | 1209 | 447 | 1656 | |
| | | Percent | 73.0% | 27.0% | 94.1% | |
| **Myalgia** | Yes | Number | 367 | 117 | 484 | 0.183 |
| | | Percent | 75.8% | 24.2% | 27.5% | |
| | No | Number | 926 | 350 | 1276 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Percent | 72.6% | 27.4% | 72.5% | |
| **Loss of consciousness** | Yes | Number | 31 | 73 | 104 | <0.001 |
| | | Percent | 29.8% | 70.2% | 5.9% | |
| | No | Number | 1261 | 394 | 1655 | |
| | | Percent | 76.2% | 23.8% | 94.1% | |
| **Nausea** | Yes | Number | 182 | 33 | 215 | <0.001 |
| | | Percent | 84.7% | 15.3% | 12.2% | |
| | No | Number | 1110 | 434 | 1544 | |
| | | Percent | 71.9% | 28.1% | 87.8% | |
| **Nausea** | Yes | Number | 121 | 19 | 140 | <0.001 |
| | | Percent | 86.4% | 13.6% | 8.0% | |
| | No | Number | 1171 | 448 | 1619 | |
| | | Percent | 72.3% | 27.7% | 92.0% | |
| **Weakness and lethargy** | Yes | Number | 260 | 53 | 313 | <0.001 |
| | | Percent | 83.1% | 16.9% | 17.8% | |
| | No | Number | 1033 | 414 | 1447 | |
| | | Percent | 71.4% | 28.6% | 82.2% | |
| **Sore throat** | Yes | Number | 51 | 8 | 59 | 0.024 |
| | | Percent | 86.4% | 13.6% | 3.4% | |
| | No | Number | 1241 | 459 | 1700 | |
| | | Percent | 73.0% | 27.0% | 96.6% | |
| **Neurological symptoms** | Yes | Number | 14 | 3 | 17 | <0.001 |
| | | Percent | 82.0% | 17.0% | 0.9% | |
| | No | Number | 1278 | 462 | 1740 | |
| | | Percent | 73.0% | 26.0% | 99.0% | |

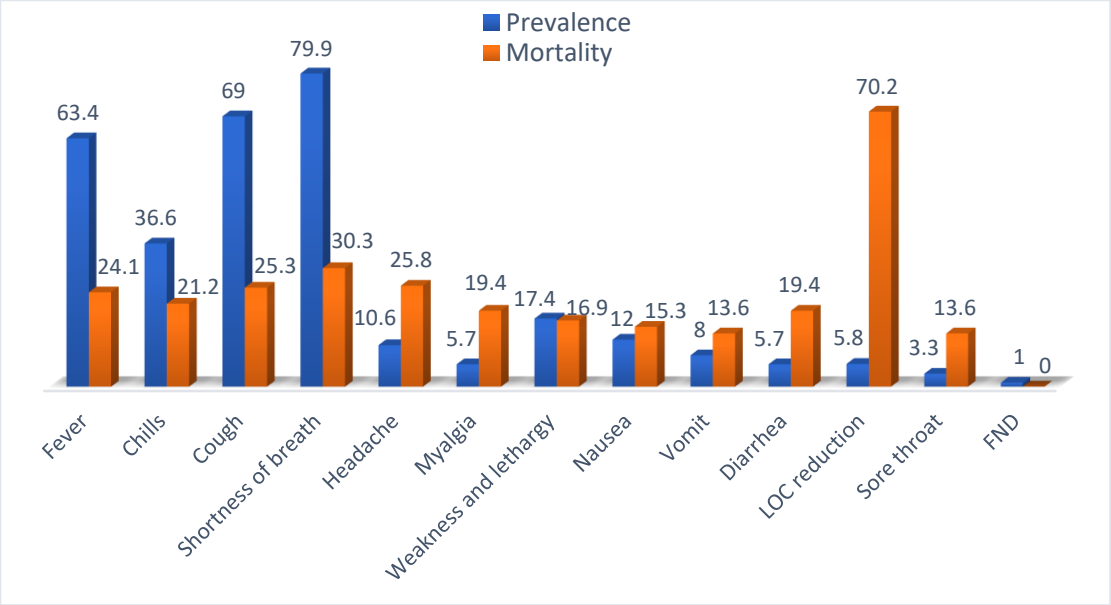


**Figure 3.** Prevalence of symptoms in patients and mortality.

O2 saturation of hospitalized patients was in the range of 40 to 100% and the maximum recorded number (mode) was 97%. Considering the cut-off of 93% in this variable; The mortality rate among patients with an oxygen saturation capacity of less than 93% at the time of admission was 36.5% and the mortality rate of patients admitted with O2 saturation above 93% was 12.9%. There was a statistically significant relationship between these two variables (P <0.001). Therefore, less than 93% O2 Saturation is associated with higher mortality.

According to Table 4 and considering the cut-off of 3 days for hospitalization, among the total deaths of 160 patients out of 3 patients who were hospitalized for more than 3 days, 160 patients (73.7%) had O2Saturation less than 93% 204 patients (82.9%) had 3 days of hospitalization, less than 93% had O2 saturation. As a result, hospitalization for less than 3 days and O2 saturation less than 93% have a statistically significant relationship with mortality outcome. On the other hand, among the total patients who were hospitalized for less than 3 days, 52.4% had less than 93% O2 Saturation and among the total patients who were hospitalized for more than 3 days, 59.4% had less than 93% O2 Saturation. Therefore, hospitalization for more than 3 days has a statistically significant relationship with O2 Saturation and worse (Figure 4).

**Table 4.** Frequency of patients by day of hospitalization and blood oxygen level at referral in terms of outcome

| Consequences | Duration of hospitalization (days) | | O2 saturation | | Total | P-value |
|---|---|---|---|---|---|---|
| | | | ≤93% | >93% | | |
| Recovery | ≤3 | Number | 183 | 309 | 492 | <0.001 |
| | | Percent | 37.1% | 62.8% | 27.8% | |
| | >3 | Number | 450 | 359 | 809 | |
| | | Percent | 55.6% | 44.3% | 45.8% | |
| Death | ≤3 | Number | 204 | 42 | 246 | 0.017 |
| | | Percent | 82.9% | 17.0% | 13.9% | |
| | >3 | Number | 160 | 57 | 217 | |
| | | Percent | 73.7% | 26.2% | 12.3% | |
| Total | ≤3 | Number | 387 | 351 | 738 | 0.004 |
| | | Percent | 52.4% | 47.5% | 41.8% | |
| | >3 | Number | 610 | 416 | 1026 | |
| | | Percent | 59.4% | 40.5% | 58.1% | |

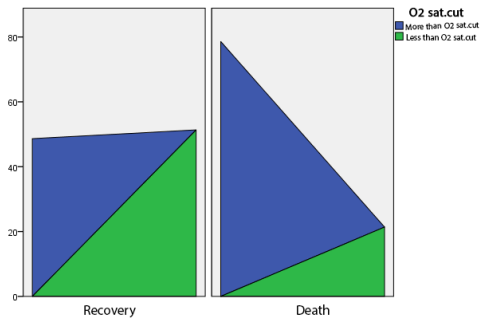


**Figure 4.** Comparison of different outcomes based on 93% cutoff for O2saturation.

According to Table 5; 750 patients underwent CT scan of the lungs, of which 96.5% (724 cases) had respiratory tract lesions according to COVID-19. This number is equivalent to 40.3% of the total number of cases under study. The mortality of these cases was 16.2%. CT scan of 26 cases (the remaining 3.5% of this group) did not show any positive results in favor of COVID-19 pulmonary involvement, but 15.4% of these cases died. There was no statistically significant relationship between positive findings in this imaging and mortality.

For 375 patients, a plain chest X-ray was performed. 248 cases (66.1%) had positive results in favor of COVID-19. The mortality rate in this group was 21.4% and among those whose chest X-ray findings were not consistent with COVID-19, it was 4.7%. . There was a statistically significant relationship between positive findings in plain chest radiography and mortality (P <0.001); Patients with lung involvement in plain chest X-ray had a higher mortality rate than patients without this involvement (21.4% vs. 4.7%).

PCR was performed for 505 patients, which was positive in 350 cases (69.3%) and negative in 155 cases (30.7%). Of those whose PCR was positive, 75.1% died. This ratio was 71.6% among those whose PCR test was negative and there was no statistically significant relationship between the positive result of this test and death outcome (Figure 5).

**Table 5.** Frequency distribution of diagnostic modalities in terms of outcome.

| Diagnostic modality | | | Consequences | | Total | P-value |
|---|---|---|---|---|---|---|
| | | | Recovery | Death | | |
| **Lung CT scan involvement in favor of COVID-19** | Yes | Number | 607 | 117 | 724 | 1.000 |
| | | Group percentage | 83.8% | 16.2% | 100.0% | |
| | | Total percentage | 80.9% | 15.6% | 96.5% | |
| | No | Number | 22 | 4 | 26 | |
| | | Group percentage | 84.6% | 15.4% | 100.0% | |
| | | Total percentage | 2.9% | 0.5% | 3.5% | |
| **Total** | | Number | 629 | 121 | 750 | |
| | | Percent | 83.9% | 16.1% | 100.0% | |
| **Chest involvement in favor of COVID -19** | Yes | Number | 195 | 53 | 248 | <0.001 |
| | | Group percentage | 78.6% | 21.4% | 100.0% | |
| | | Total percentage | 52.0% | 14.1% | 66.1% | |
| | No | Number | 121 | 6 | 127 | |
| | | Group percentage | 95.3% | 4.7% | 100.0% | |
| | | Total percentage | 32.3% | 1.6% | 33.9% | |
| **Total** | | Number | 316 | 59 | 375 | |
| | | Percent | 84.3% | 15.7% | 100.0% | |
| **PCR** | Yes | Number | 87 | 263 | 350 | 0.441 |
| | | Group percentage | 24.9% | 75.1% | 100.0% | |
| | | Total percentage | 17.2% | 52.1% | 69.3% | |
| | No | Number | 44 | 111 | 155 | |
| | | Group percentage | 28.4% | 71.6% | 100.0% | |
| | | Total percentage | 8.7% | 22.0% | 30.7% | |
| **Total** | | Number | 131 | 374 | 505 | |
| | | Percent | 25.9% | 74.1% | 100.0% | |

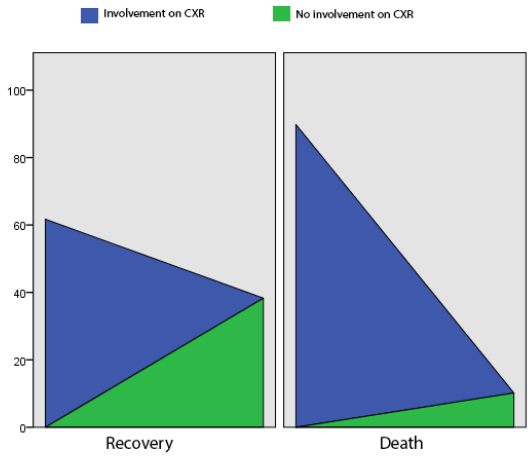


**Figure 5.** Comparison of different implications in chest radiography.

According to the information recorded in medical records and according to Table 6; Only 19 patients underwent all three methods of PCR, CXR and CT Scan Chest. In 6 patients (31%), the findings of all three methods were positive for COVID-19, of which 1 (16%) died and 5 (83%) recovered. In 7 patients (36%) PCR and CT scan findings were positive and CXR findings were negative, of which 1 patient (14%) died and 6 patients (85%) recovered. In total, in 1 patient (5%) only CT scan was positive and was associated with improved outcome. Also, the number of patients who had only positive PCR was 1 (5%) who had recovery. 4 patients (23%) had positive CXR and CT scan findings and negative PCR and all 4 patients had recovery. No significant relationship was found between the mentioned statistical information.

**Table 6.** Outcome assessment among diagnostic methods performed.

| Group | | Consequences | | Total |
|---|---|---|---|---|
| | | Death | Recovery | |
| **Involvement of CXR and chest CT with positive PCR** | Number | 1 | 5 | 6 |
| | Group percentage | 16% | 83% | 100% |
| | Percentage in outcome | 50% | 29% | 31% |
| **No CXR involvement with chest CT and PCR positive involvement** | Number | 1 | 6 | 7 |
| | Group percentage | 14% | 85% | 100% |
| | Percentage in outcome | 50% | 35% | 36% |
| **No CXR involvement with chest CT and negative PCR involvement** | Number | 0 | 1 | 1 |
| | Group percentage | 0% | 100% | 100% |
| | Percentage in outcome | 0% | 5% | 5% |
| **No involvement of CXR and chest CT with positive PCR** | Number | 0 | 1 | 1 |
| | Group percentage | 0 | %100 | 100% |
| | Percentage in outcome | 0% | 5% | 5% |
| **CXR and chest CT involvement with negative PCR** | Number | 0 | 4 | 4 |
| | Group percentage | 0% | 100% | 100% |
| | Percentage in outcome | 0% | 23% | 21.1% |
| **Total** | Number | 2 | 17 | 19% |
| | Group percentage | 10% | 89% | 100% |
| | Percentage in outcome | 100% | 100% | 100% |

## Discussion

In a cross-sectional analytical study, after obtaining permission from the ethics committee in the research department of Guilan University of Medical Sciences, a list of all cases admitted to Corona with suspicion during February and April 2020 in Razi Educational and Medical Center in Rasht was prepared. The list included 1,796 patients. The outcome of 4 patients in the files was not known and 1792 cases entered the statistical analysis process. The mortality rate was 484, representing 27% of the study population. In a study by Tehrani S et al. In Karolinska, Sweden, on 255 patients, 27% died. Most deaths occurred during hospitalization and within the first 30 days. The reason for the high mortality rate of this study was the lack of use of corticosteroids or other specific treatments that were later proven to be effective. In this study conducted in Karolinska, 90% of deaths were observed among patients 65 years and older (44% mortality rate) (7). In a British study of 20133 hospitalized patients with COVIDium 19, this rate was 26% (8).

The overall mortality rate based on inpatients and outpatients in the study of Nikpouraghdam et al., Was estimated to be 1.85%. This rate was 8.06% in hospitalized patients (9). In a study by Zhonghua et al., The mortality rate of critically ill patients hospitalized in China was reported to be over 49% (10). In a study of 22,512 patients in Italy, the overall mortality rate in COVID-19-confirmed patients was 7.2%. This value was 2.3% in China (11).

Of these deaths in our study, 263 were positive PCRs and were considered definitive COVID. If we consider the mortality of 2.3% for this disease, this number of PCR feet (positive and total death) in proportion to the representative of 11 to 21 thousand are affected, and a high percentage of this number of people are asymptomatic or have mild and actual symptoms. There were reservoirs of disease in the community, a conclusion that can be disputed with the results of a study by Hu et al. In the Hu study, the results showed that among those in close contact with a definite case of COVID who were examined and their PCR results were positive, 20.8% had a short interval, 50% had positive CT findings, while 20.8% of these cases were never symptomatic; These populations were significantly younger (12). Considering that all medical centers in Rasht at that time had dedicated special wards to patients suspected of having COVID-19, we suggest that a similar study be performed in all centers and by combining the results of these studies and conducting a review study. A clearer picture of the disease situation at that time can be obtained. In this study, 58.3% of hospitalizations and 65.1% of deaths were male OR (1.85:1). A total of 30.1% of hospitalized men and 22.6% of hospitalized women died. Similar findings were found in many studies (13, 14). Also, during the results of Nikpouraghdam M study with Logistic Regression analysis, age, male gender and underlying diseases have a significant effect on mortality in COVID-19 patients (5018 In MERS and SARS, men were more affected than women (15). Women are less likely to be infected due to the X chromosome and sex hormones that affect innate acquired immunity (16). According to Sunil S. Bhopal et al. study, although the number of male patients was not different from the number of female patients, COVID-19 mortality was twice as high in men as in women, which could be due to genetic and lifestyle differences (such as occupation, cigarettes and alcohol) and cultural and social differences. Of course, it is worth noting that the mortality rate of men to women in different age groups is different, for example, during this study, the mortality rate of men to women in the age group of 0-9 years was 0.8, while in the age group of 60-69 years 2 .6 was obtained (17). In the study of Caizheng Yu et al., The median age was 64.0 years (18). With increasing age and more production of type B cytokines, T-cell and B-cell function is impaired and causes a worse prognosis in elderly patients. In general, higher mortality in men can be due to social and economic factors and a more prominent presence of men in bioeconomic and social (19, 20).

The higher mortality of the rural population is consistent with the results of the Khan study. In Khan's study, this issue, which does not seem to be consistent with population density and the spread of more disease in cities, was attributed to the cumulative effects, differences and discrimination between urban and rural area (21).

Higher mortality in opium use indicates the association between opium use and the severity of the disease when hospitalized. These results are similar to the results of

a meta-analysis performed in China (22). We suggest comparing the course and clinical status of COVID-19 in these patients and comparing it with patients who are not addicted to opium and smoking. The results of such a study can be used to inform the whole community and create a negative factor about addiction.

21.1% of the total population have been hospitalized and died with a history of underlying disease. The most common diseases included hypertension and diabetes. 38.3% of all deaths were due to this disease, if this statistic is combined with the fact that 75% of people with improved blood pressure do not have the disease, the impact of this disease on more severe cases and weaker consequences associated with this disease can be Analyzed. In our study, there was a statistically significant relationship between hypertension and death outcome (P <0.001). In various studies such as meta-analysis by Yang et al. And meta-analysis by Zheng et al., The underlying diseases of diabetes, hypertension, cardiovascular disease and hyperlipidemia have been associated with a worse prognosis (23, 24). In our study, the highest death rate was among cancer patients undergoing radiotherapy, with 66.7% of the population dying. After that were patients with liver disease (57.9% feet, P <0.05) Next ranks of cancer (56.1%) Chemotherapy (43.3%) Neurological diseases (44.4%) History of CVA ( 40%), cardiovascular diseases (36.5%) and the use of immunosuppressive drugs (36.5%), respiratory diseases (34.3%), organ transplants (35.1%) and diabetes (32%). All of these are significantly associated with a weaker immune response to the presence of an infectious agent in the body. Also in the study of Chirag Shah et al., Kidney and heart disease were significantly associated with COVID's mortality (13)

Many other studies have shown an association between the incidence of Acute Kidney Injury and coronary mortality (25). Although the mechanism of kidney damage has not been elucidated in COVID-19, many studies have suggested an association between renal involvement and SARS-CoV-2 (26, 27).

In the Tehrani S. study, chronic kidney disease and previous (old) stroke are independent risk factors for coronary mortality. The association between previous stroke and mortality of COVID-19 may be due to disabilities or a high risk of coagulation disorders. The two most common underlying diseases in this study were hypertension (54%) and diabetes (31%) (7). This finding was confirmed by other studies (28, 29).

In some studies, hypertension was identified as an independent risk factor for severe COVID-19. It should be noted, however, that hypertension is a common disease worldwide with an incidence of 78% in people aged 65 to 74 in Sweden. After statistically adjusting for age, they found that there was no relationship between blood pressure and mortality (30).

Other studies confirm the findings that people with underlying diseases such as cardiovascular disease, hypertension, diabetes, congestive heart failure, cerebrovascular disease, chronic kidney and liver disease, cancer, COPD, asthma and HIV / AIDS have a higher risk of death from COVID-19 (31). As the number of articles and studies published increases, so does the difference between the results obtained. Some have confirmed the link between COVID-19 mortality and the underlying disease, and some have denied it. On the other hand, it is clear that in regions with higher mortality rates (such as the United States, Europe and China), the prevalence of underlying diseases was generally higher than in other regions (32). The SARS-CoV-2 virus is activated by ACE2, which binds to cells. ACE2 is expressed on heart, kidney and type 2 alveolar cell (33). There is a hypothesis that prior use of ARBs can increase ACE2 at the cellular level, leading to more morbidity and mortality in people with ARBs underlying diseases (34). The results of a meta-analysis by Ssentongo P. et al. Show that people with COVID-19 with cardiovascular disease, hypertension, diabetes, congestive heart failure, chronic kidney disease, and cancer are at higher risk for COVID-induced death. There are 19. According to this meta-analysis, patients with COVID-19 who have cardiovascular disease are twice as likely to die (35).

Another possible hypothesis for a high risk of mortality in patients with the underlying disease could be due to body depletion or allostatic load. In other words, chronic diseases disrupt the physiological function of the body and result in the accumulation of pro-inflammatory cytokines. These cytokines affect the cellular immune system. Due to the weakened immune system, these patients are at risk for severe forms of COVID-19 disease and death (36).

In the Yang JK study, plasma glucose levels and diabetes were independent predictors of mortality in SARS. In diabetic patients, affinity for cell binding and virus entry into the cell and the risk of cytokine syndrome are higher, virus clearance and T-cell function are lower (37).

Many of these diseases are strongly associated with the patient's lifestyle and are the result of the accumulation of the effects of various factors such as genetics, nutrition, mobility, smoking and drugs, the final effect of which usually occurs after prolonged exposure to risk factors. Considering the profound effect of this pandemic on human morale and following the news and cases related to this disease, a study can compare the effects of this disease between this group and healthy people without a history of underlying disease and by including items such as regular exercise. Mobility rate, consumption of fruits and vegetables among the study variables provided significant information to the community. Such studies will have a strong impact on the approach and mindset of the country's population in the present time. Indeed, an accident (pandemic) is not reported, but getting ready to increase the chance of survival is a human preoccupation.

Among the symptoms studied in this study, a group of symptoms that referred to pulmonary involvement, including shortness of breath and low O2Sat, along with a history of altered level of consciousness, were associated with worse outcomes, while constitutional symptoms and gastrointestinal symptoms were associated with improvement. These results are consistent with the results of a study by Zheng et al. In his study, often respiratory symptoms at the time of admission were associated with a worse prognosis (22). In our study, the worst symptom was a decrease in the patient's level of consciousness, which occurred in 70.2% of cases of hospitalization of patients with this symptom.

The main manifestation of COVID-19 during this pandemic was respiratory symptoms associated with hypoxia, followed by respiratory failure and mechanical support and extracorporeal failure (38). Of the two predictors, at least O2Saturation is stronger. Maximum body temperature during hospitalization is also an important predictor. However, not all patients with fever present (26). In a study by Z. Wu et al., Out of 44500 definitive cases of COVID-19, 80% presented with mild respiratory symptoms and 19% with severe respiratory symptoms and severe illness including respiratory failure. Some patients also progressed to severe complications, including multiple organ failure, septic shock, pulmonary edema, severe pneumonia, acute respiratory syndrome, and death (39).

Identifying predictors can help physicians prioritize patients and assign treatment options as well as vaccines.

During the Shah C. study, respiratory symptoms were the most common manifestation among deceased patients (72.11% shortness of breath, 51.70% cough). Also, the percentage of patients who initially presented with positive imaging findings was higher among the death group (82.31%). The incidence of active cancer was higher in the group of deaths, but this variable could not predict the mortality of COVID-19 due to the small number of samples (13).

In the Mehraeen E. 10 study, the most common manifestations in 310494 COVID-19 patients were fever, cough, olfactory dysfunction, postnasal drip, taste disturbance, and nasal obstruction (14).

In Iran, a study was performed on 2964 patients with COVID-19 admitted to the hospital between February to April 2020 (approximately corresponding to the time of this study) and showed that 14% of COVID-19 patients had a serious disease and 6 Severely ill and a total of 20% needed hospitalization. Among 239 feet, 66.94% were 60 years of age or older and 15.89% had underlying disease (such as diabetes, hypertension, and chronic lung disease, etc.) (9).

In a study, by separating the two populations, the difference in outcome and the relationship between different symptoms and the severity of the disease can be investigated. The results of such a study will be useful in setting a more up-to-date guideline in dealing with patients suspected of having COVID-19.

The use of paraclinical methods in the diagnosis and prognosis of the disease is helpful in many clinical conditions. In this study, lung involvement in plain chest radiography was most strongly associated with mortality. Comparison of CT scan and PCR results

showed no statistically significant relationship between their positivity and death. Whereas in plain chest X-ray data, only 4.7% of cases whose CXR lacked evidence of pulmonary involvement died.

A study by Tabatabaei S. et al. Showed that CT Scan severity, based on parenchymal involvement, could be a good predictor of mortality in healthy adolescents with COVID-19 pneumonia. Young patients are often healthy and present with shortness of breath and a mild fever, but their disease may worsen over time. This study emphasizes that in CT Scan reports, the number of lobes involved and the severity of the involvement along with its morphological pattern must be mentioned in order to measure the severity of the disease (40). Although routine use of CT scans to detect COVID-19 is not recommended, many studies have suggested its role in the follow-up of patients (40). Due to the higher cost of CT scans, it is recommended that after a thorough examination of the lungs to check for the presence and extent of pulmonary involvement, CXR is recommended. In the case of PCR, the high mortality rate among PCR-negative individuals and the lack of statistical differences between PCR-positive and PCR-negative deaths, it seems that the PCR result should have been more positive (41). It is recommended that a study be performed on the knowledge of the treatment staff about how to properly take and maintain the sample to evaluate SARS-CoV2. It is also possible to design and conduct a study to review the results presented by different laboratories to analyze the amount of error in both sampling and sample review. Also, due to the cluster spread of this disease among families and the existence of a very significant number of asymptomatic carriers of COVID-19, it is possible to randomly select several COVID-19 patients and perform PCR test among their asymptomatic family members. With a short two-week follow-up, it is possible to identify a proportion of asymptomatic people and inform the community of the danger that threatens them by publishing the results.

In our study, 86.7% of ICU patients died, which is consistent with Shah C.'s study. The ratio of the number of patients admitted to the ICU in the death group was higher than the recovery group (23.13% vs. 6.18%). Patients in the death group were older than the recovery group (mean 78.4 vs. 64.1) (13).

## Conclusions

The results of the present study showed that male gender, older age, history of the underlying disease, simple chest X-ray involvement, drug use and pulmonary symptoms were associated with more adverse outcomes and natural and gastrointestinal symptoms were associated with improved outcomes in patients with COVID-19.

### Author contribution

**MRT** managed the manuscript, study design, controlling the project and fulfilled the data processing and compiled some sections of the article. **AM**, **AB**, **HMK**, **SI**, **JK**, **SNS**, **FS**, **EBA** and **HEK** were involved in some sections of the manuscript like collected data, data processing and performed statistical analyses. All authors revised the article comprehensively and confirmed the final edited version of the paper

### Conflict of interest

No potential conflict of interest was reported by the authors.

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# Kyphosis and Carrying Angle: Prevalence and correlation between anthropometric features

Daniel Rahimi Nejat [1], Sheyda Rimaz [2], Arad Kianoush [1], Masoumeh Faghani [3] *

[1] Student Research Committee, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

[2] Student Research Committee, School of Medicine, Anzali International Campus, Guilan University of Medical Sciences, Rasht, Iran

[3] Department of Anatomical Sciences, School of Medicine, Guilan University of Medical Sciences, Rasht, Iran

## Abstract

**Introduction:** Kyphosis is the spinal curve that causes the top of the back to seem abnormally rounded. Carrying angle can be measured with the upper limb being fully extended. The study aim was determining the mean and correlation between kyphosis and carrying angle with demographic factors in medical students of Guilan University of Medical Sciences.

**Materials and Methods:** In this observational study, we assessed asymptomatic young adults in their first three years of enrollment in medical school. The participants had neither current nor a history of spinal or upper arm injuries. Kyphosis and carrying angle were measured by using the Debrunner kyphometer and goniometer, respectively. We also measured anthropometric features such as weight and height.

**Results:** We studied 217 medical students (M/F= 1.17/1), with a mean age of 21.43±2.06. Kyphosis has a statistically significant negative correlation with height, weight, and carrying angle of both dominant and non-dominant upper limbs. We found kyphosis to be greater in female than in male participants. Carrying angle was greater in the dominant upper limb than the non-dominant upper limb. Dominant upper limb carrying angle was also positively correlated with height and weight.

**Conclusion:** In asymptomatic young adults with no history of spinal diseases, anthropometric features such as height and weight impact kyphosis angle. It seems that kyphosis is greater in females. Severe changes in kyphosis angle may cause loss of sagittal orientation. We suggest that people at risk of kyphosis be screened in early adulthood to prevent the increase of kyphosis and its subsequent complications.

**Keywords:** Kyphosis, Carrying angle, Asymptomatic young adults, Anthropometric features

*Corresponding Author: Masoumeh Faghani

✉ Email: mfaghani2000@gmail.com

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## Introduction

The back is described as the posterior aspect of the body and provides the trunk with a musculoskeletal axis (1); The main component of the back is the vertebral column which consists of 33 vertebrae and is divided into cervical, thoracic, lumbar, sacral, and coccygeal regions (1).

In the coronal plane, the vertebral column is positioned in the body's midline. When viewed in the sagittal plane, it has a number of curvatures. The primary curvature is an outward curve reflecting the embryo's kyphotic posture. This kyphotic curve remains in adults' thoracic and sacral regions (1).

The two secondary curvatures, which are formed in the cervical and lumbar regions, are inward curves; they occur as one holds up its head and stands upright, respectively. These, along with the primary curves, bring the body's center of gravity into a vertical line, which leads to maintaining an upright bipedal stance with the least amount of muscular energy (1,2).

The spinal curve that causes the top of the back to seem abnormally rounded is described as kyphosis (2). Kyphosis has several etiologies; it can occur due to developmental anomalies such as Scheuermann's disease, or it can be congenital(3). Secondary etiologies include trauma, degenerative disc disease, inflammatory disease, muscular and neuromuscular diseases, tumors and pathologies, osteoporotic burst or compression fractures(4). Kyphosis may also develop due to iatrogenic reasons such as inappropriate surgical procedures resulting in the flatback phenomenon or post-laminectomy syndrome (5). Regardless of the etiology, the eventual outcome is loss of sagittal orientation resulting in back pain, instability of the spinal structure, or clinical deformity.

Several factors may alter the thoracic kyphosis degree. These include anthropometric features (6,7), BMI (8), gender and age (6), performing exercise (9,10),

Mid-High-Heeled Footwear (11), transporting an infant (12) or a backpack (13,14).

Most of the papers studying kyphosis are related to scoliosis, lumbar lordosis, or other deformities related to the etiology and surgery of kyphosis (15–17). Some studies showed that the spinal column could be considered a linear chain linking the head to the pelvis. With the change of each vertebral curve, the rest of the curves try to change along to maintain the linear chain and orientation of the spinal column (18). Another body anthropometric feature that may also impact thoracic kyphosis is elbow carrying angle; neither its average value has been studied in our community nor its correlation with thoracic kyphosis.

When the elbow joint is fully extended, the forearm and arm will not align in a straight line. The long axis of the extended forearm lies at an angle to the long axis of the arm. This angle, which opens laterally, is called the carrying angle and is about 10° in the male and 13° in the female. The angle disappears when the elbow joint is fully flexed (19).

The presence of anthropometric information in different races and regions of the world about the natural range of thoracic kyphosis and the carrying angle may be helpful to the clinicians in planning the correction of skeletal deformities and assessing the related pathological conditions. Medical clinical procedures are based on descriptive and epidemiology data. There is no epidemiological information on the prevalence of kyphosis and the carrying angle in Guilan province, especially among medical students. On the other hand, the sitting patterns of most of the students are incorrect when they are studying. To our knowledge, no study has yet evaluated the thoracic kyphosis and elbow carrying angle and the relationship between them in the medical students. Therefore, this study investigates the carrying angle, kyphosis, and their relationship with demographic factors in the first three years of asymptomatic medical students.

## Materials and Methods

This observational study was carried out on 217 asymptomatic young adults who were randomly recruited from their first three-year medical students. The participants consisted of 100 females and 117 males, and their ages ranged from 18 to 32 years old. Inclusion criteria were: medical students in the first three years of their study, absence of current or history of spinal column or upper arm fracture or disease. Exclusion criteria were: history of spinal column or upper arm fractures or diseases.

The study was approved by the ethics committee of Guilan University of Medical Science (No: IR.GUMS.REC.1397.162). The purpose of the study was explained to all of the participants, and they signed an informed consent form.

Kyphosis was measured using Debrunner kyphometer and the carrying angle using goniometer following the methods, which will be explained in the following.

The Debrunner kyphometer consists of two parallel arms connected with a 1° scale protractor. The reliability and validity of this device are considered to be high, with intra-rater reliability of 0.98 compared to the Cobb angle (20). On each of the other ends of these two arms is a block that will be placed on spinous processes of the upper and lower limits of the thoracic spine, and the kyphosis degree appeared subsequently on the protractor to be read. The spinous processes were localized by palpation. The examiner localized the C7 spinous process; the subject was asked to look down and then look forward again slowly. The most prominent process at the lower end of the neck is the C7, and a marking was done by a pen. The T12 spinous process was then localized by counting down the spinous processes with the subject asked to lean forward and round its back outward and towards the examiner. The T12 is about four vertebrae beneath the end point of scapula. Again, a marking was done with a pen. Following the marking, the subject was asked to stand barefoot in a neutral posture with the arms swinging at the sides and was then asked to look forward. The end blocks of the upper and lower arms were directly placed over the C7 and T12 spinous processes, respectively; the kyphosis angle that appeared on the protector was read subsequently. Each measurement procedure was repeated twice, and if any of the three measurements differed by more than 5°, all three markings and measurements were repeated. The average was the primary value (20).

In order to measure the carrying angle, the subject was asked to stand in anatomical position; the elbow extended completely and the forearm supinated fully. The goniometer's upper arm and lower arm were aligned with the direction of the subject's upper arm and forearm, respectively. Then, the angle on the measurement plate placed on the elbow was read. The measurement was done on each side three times to minimize measurement errors, with the average being the primary value (21). Height and weight were recorded for BMI assessment. All the information was recorded for further evaluations.

The research team received the same measurement protocol instruction from the anatomic faculty member (M. Faghani), including skeletal anatomy review; instruction in finding landmarks by palpation; illustration of how to place the kyphometer and read the kyphosis angle on the device's protractor; illustration of how to place the goniometer and read the carrying angle on the instrument's measurement plate.

The data are represented as mean ± standard deviation (SD). Statistical analysis was performed using SPSS 21 (SPSS Inc, Chicago, IL, USA). Analysis of the difference between mean values of the groups was performed using T-test and One Way ANOVA. A P value smaller than 0.05 was considered meaningful. The correlation between qualitative and quantitative variables was assessed through Chi-square and Pearson's Correlation Coefficient, respectively. The difference between the groups in terms of kyphosis and carrying angle and clinical parameters and the correlation and relationship between kyphosis and carrying angle and the dominant upper limb were analyzed.

## Results

217 medical students, including 117 men (53.9%) and 100 women (46.1%), participated in this study. The participants were 18-27 years (21.43 ± 2.06). 129 participants had a BMI of 19-25 (table1). 89.9% of the participants were right-handed, and 10.1% were left-handed. The mean and SD of carrying angle in the dominant upper limb was 14.26 ± 4.5 (max 26.67, min 4.33).

**Table 1.** Demographic information of medical students of Guilan University of Medical Sciences in this study.

| Variable | Condition | Number | Percent |
|---|---|---|---|
| **Gender** | Male | 117 | 53.9% |
| | Female | 100 | 46.1% |
| **Age** | 21 or less | 126 | 58.1% |
| | More than 21 | 91 | 41.9% |

| | | | |
|---|---|---|---|
| **Mean Age ± SD (min – max)** | | 21.43±2.06 (27-18) | |
| **BMI** | 19≥ | 29 | 13.4% |
| | 25 – 30 | 45 | 20.7% |
| | 30< | 14 | 6.5% |
| **Mean BMI ± SD (min-max)** | | 23.22±3.82 (15.97-40.56) | |
| **Mean Height ± SD (min-max)** | | 171.4±9.29 (195-152) | |
| **Mean Weight ± SD (min-max)** | | 68.55±14.28 (42-122) | |
| **Dominant Upper Limb** | Right | 195 | 89.9% |
| | Left | 22 | 10.1% |

We found a statistically significant difference between the degree of the carrying angle of the dominant and non-dominant upper limbs using T-test (t= 5.4, P= 0.0001); the carrying angle was found to be greater in the dominant upper limb (Mean±SD=14.26±4.5) compared to the non-dominant upper limb (Mean±SD=12.11±3.74).

Using Chi-square, the data revealed a statistically significant relation between kyphosis and gender (P=0.0001), but no relation between kyphosis and age (P=0.456) or BMI (P=0.606). Kyphosis was found to be greater in women than men (Table 2).

**Table 2.** Comparison of kyphosis in medical students according to demographic characteristics.

| Variables | Groups | Kyphosis>25° | | Kyphosis<25° | | P value |
|---|---|---|---|---|---|---|
| | | Number | Percent | Number | Percent | |
| **Gender** | Male | 33 | 28.2% | 84 | 71.8% | P=0.0001 |
| | Female | 76 | 76% | 24 | 24% | |
| **Age (years)** | 21≥ | 66 | 52.4% | 60 | 47.6% | P=0.456 |
| | 21< | 43 | 47.3% | 48 | 52.7% | |
| **BMI** | 19≥ | 13 | 44.8% | 16 | 55.2% | P=0.606 |
| | 19-25 | 67 | 51.9% | 62 | 48.1% | |
| | 25-30 | 24 | 53.3% | 21 | 46.7% | |
| | 30≤ | 5 | 35.7% | 9 | 64.3% | |
| **Dominant Limb** | Right | 98 | 50.3% | 97 | 47.7% | P=0.982 |
| | Left | 11 | 50% | 11 | 50% | |

We found a negative correlation between kyphosis and height (P=0.0001) and weight (P=0.0001) of the participants; a decrease in both height and weight was correlated with an increase in kyphosis (Table 3). In addition, we found that the increase in the weight (P=0.0001) and height (P=0.0001) of the medical students in this study was correlated with an increase in the carrying angle of the dominant upper limb (Table 3).

**Table 3.** The correlation between kyphosis, dominant upper limb carrying angle with some quantitative variables of demographic characteristics.

| Variables | | Kyphosis angle | Dominant Upper Limb Carrying Angle |
|---|---|---|---|
| **Age (year)** | Pearson Correlation | -0.124 | -0.1 |
| | P-Value | P=0.069 | P=0.144 |
| | correlation | No correlation | No correlation |
| **BMI** | Pearson Correlation | -0.006 | 0.132 |
| | P-Value | P=0.93 | P=0.053 |
| | correlation | No correlation | No correlation |
| **Height (cm)** | Pearson Correlation | -0.45 | 0.4 |
| | P-Value | P=0.0001 | P=0.0001 |
| | correlation | Negative correlation | Positive correlation |
| **Weight (kg)** | Pearson Correlation | -0.237 | 0.309 |
| | P-Value | P=0.0001 | P=0.0001 |
| | correlation | Negative correlation | Positive correlation |

The analysis of data with Pearson's Correlation Coefficient revealed a negative correlation between the kyphosis and the carrying angle of the both dominant (P=0.0001) and non-dominant (P=0.01) upper limbs of the participants; which means the increase of kyphosis was correlated with the decrease of the carrying angle in both dominant and non-dominant upper limbs of the participants (Figure1).

As a means to predict kyphosis using multivariate regression, all variables related and correlated to kyphosis were put into a prediction model. The results showed that the height and the dominant upper limb carrying angle have an intervening and predictive role (Table 4). Therefore kyphosis can be predicted using the following formula:

Kyphosis= 81.28 -0.311×height(cm)- 0.327×dominant upper limb carrying angle.

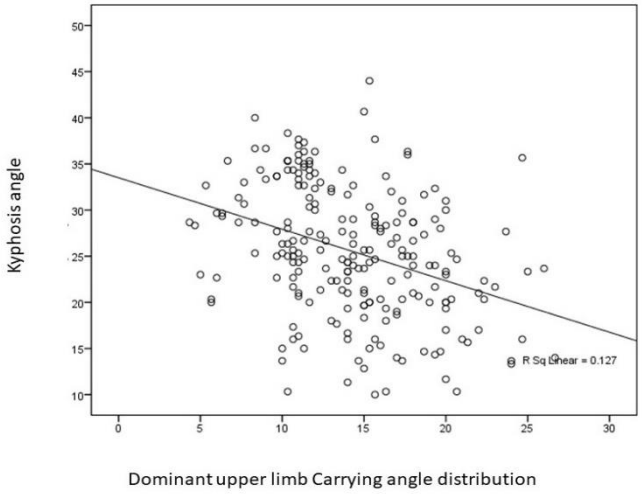


**Figure 1.** Distribution diagram and regression line of Kyphosis Angle with Dominant Upper Limb Carrying Angle Distribution.

**Table 4.** Correlation of the demographic characteristics and kyphosis in adjusted and unadjusted multiple logistic regression model.

**Coefficients[a]**

| Model | Unstandardized Coefficients | | Standardized Coefficients | t | Sig. |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | | |
| **(Constant)** | **81.289** | **9.141** | | **8.893** | **0.000** |
| Height (cm) | **-0.311** | **0.062** | **-0.409** | **-5.055** | **0.000** |
| Weight (kg) | **0.036** | **0.038** | **0.073** | **0.957** | **0.340** |
| The angle of deviation of the dominant hand (degrees) | **-0.327** | **0.137** | **-0.209** | **-2.385** | **0.018** |
| The angle of deviation of the non-dominant hand (degrees) | **-0.018** | **0.155** | **-0.010** | **-0.118** | **0.906** |

**a. Dependent Variable:** Kyphosis angle

## Discussion

This study assessed the kyphosis angle and carrying angle of 217 medical students aged 18-27 years. The relation between these two parameters and other anthropometric features was examined. The participants' demographic information included their age, gender, height, weight, BMI, and dominant limb. Statistical analysis using the T-test, revealed a statistically significant difference in the carrying angle of the dominant upper limb compared to the non-dominant upper limb (t= 5.4, P= 0.0001). This finding was in line with the results of Yilmaz et al, who found that the carrying angle of the dominant arm was significantly higher than the non-dominant upper limb, regardless of gender (22).

Our study also suggests that gender, BMI and age has a statistically significant relationship with the degree of kyphosis (P=0.0001). One review study had findings that conflicted with our results, in that they found no differences between genders and kyphosis (23). This difference can be attributed to the study population, as ours only included medical students, in their first three years of enrollment, in a single university. In contrast,

Zappalá et al. (23) analyzed 34 studies in a meta-analysis with participants of various ages and ethnicity. Their study was mainly aimed at the relationship between thoracic curvature and age, gender, and race.

A strong negative correlation between the kyphosis and the carrying angle in both dominant and non-dominant upper limbs was noted. Also, a negative correlation was found between kyphosis and height and weight and a positive correlation between the carrying angle and the height and weight. Kyphosis was greater in female participants, and the carrying angle was greater in the dominant upper limb than in the non-dominant upper limb. The findings of Ruparelia et al. was similar to our study (24) who found that height had a significant correlation with carrying angle. Some studies showed that abnormal behavior such as carrying heavy objects or heavy backpacks in children, incorrect sitting or standing position can effect on the human posture (12,13). Of note, different industries can make products by using the country's anthropometric and ergonomic features to make the better equipment needed by offices, schools, and universities. Awareness of body posture changes in children and adolescents may help prevent the occurrence of musculoskeletal diseases, back pain, and degenerative changes in the spine.

One exciting aspect of our results was the predictive model for kyphosis, which was achieved through multivariate regression. The model, which shows the predictive and intervening role of height and dominant upper limb carrying angle, can potentially be helpful in application after assessing its accuracy and reliability in follow-up studies. One such potential use could predict the thoracic kyphosis in a clinical setting where neither radiographic studies nor Debrunner kyphometer is available.

There were some limitations to this study, including the small population, which only included young medical students in a single center. Conducting the study in a larger population with a broader range of ages would result in different outcomes.

## Conclusions

Overall, our findings indicate that the carrying angle of the dominant upper limb is greater than the non-dominant upper limb, gender has a statistically significant relation with kyphosis degree, and the kyphosis angle is negatively correlated with carrying angle of both upper limbs. Our findings in this study show that height and weight have a negative correlation with kyphosis and a positive correlation with the carrying angle of the dominant upper limb. We suggest that people who are at risk of developing kyphosis should be assessed during early adulthood to prevent kyphosis angle from increasing, as well as to reduce the potential complications the increase of kyphosis and carrying angle can cause, such as loss of sagittal orientation, back pain, instability of the spinal structure, and clinical deformities.

### Author contribution

**MF** supervised and managed the project and also edited and revised the manuscript. **DRN** , **ShR** , **AK** collected the data and wrote the primary draft of the manuscript.

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### Conflict of interest

There are no potential conflicts of interest.

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# Investigation of suture surgery with ant by Hakim Mohammad the Iranian surgeon of Safavid Era (1501 to 1736)

Saeed Sepehrikia [1,2], Marzieh Qaraaty [1,2] , Fatemeh Kolangi [3]*

[1] Clinical Research Development Unit (CRDU), Sayad Shirazi Hospital, Golestan University of Medical Sciences, Gorgan, Iran

[2] Department of Persian Medicine, School of Persian Medicine, Golestan University of Medical Sciences, Gorgan, Iran

[3] Counseling and Reproductive Health Research Centre, Department of Persian Medicine, School of Persian Medicine, Golestan University of Medical Sciences, Gorgan, Iran

## Abstract

Hakim Mohammad, a military physician, and surgeon of the Safavid Era (1501 to 1736) and the author of Dhakhira-Yi-Kamilah book, served as a young man in the Ottoman Empire Officer as a surgeon physician. In this study, the method of suturing by Hakim Mohammad has been introduced. Suturing with ant was a wound healing method that was carried out by Hakim Muhammad to treat the wounds of certain areas of the body, by a special species of ants called fire ants, and by the lower jaw of these ants.

Also, Hakim Mohammed suggested specific food and drug in order to take care of the wound and control infection and pain followed by this type of suture. Study of the treatment methods of predecessors shows us developments and the path to the progress of surgical affairs and can be used in the direction of further advances.

**Keywords:** Hakim Muhammad, Suture, Ant, Wound Healing, Persian Medicine

*Corresponding Author: Fatemeh Kolangi

✉ Email: dr.kolaangi@gmail.com

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## Introduction

Surgery is an important discipline in the history of medical science because it can be used to treat many different diseases (1).

The study surrounding the history of the Safavid Era in comparison with some other sciences faces special problems (2).

Medical science in the Safavid Era was generally not in the hands of trained physicians; But some physicians learned medicine wholly scientifically from a teacher and through this, and in this way, the physician, when completed his studying course, could not do treatment, especially surgery without receiving licenses (3). Among the important physicians in the Safavid Era was Hakim Bashi (court physician) had a significant and valuable place in court (4).

In this study, the way that Hakim Mohammed used to suture and the subsequent recommendations for healing wounds are addressed.

In this review, we used books and valid scientific articles, and also through search engines of Pubmed, Magiran, Sid and Google Scholar. The keywords that were searched included “Safavid Era”, “Suture”, “Wound Healing”, “Ant”, “Hakim Mohammed”, “Military Surgeon”, and “Persian Medicine (PM)”. In this research, by studying the sources and after classification and summarization, the results are presented in this paper.

**Medicine in the Safavid Era**

At the end of the fifteenth century, the Safavid dynasty built the Iranian Empire by forming a stable successful and long-term government (1501-1736)(5).

During the Safavid Era, physicians’ education was very similar to the training of surgeons, and the young physician came to the service of experienced physicians for an internship, and for this purpose, this physician was one of those who worked in hospitals (6). Medicine was important in the Safavid Era, such as other courses (7). One of the physicians of this era was Hakim Muhammad who served as a military surgeon as well as one of the physicians of Safavid Era serving the Ottoman Empire (5).

**Hakim Mohammed**

Hakim Mohammad Surgeon was contemporary with Shah Abbas ١(1571-1629) and Shah Safi ١(1611-1642). There is not enough information about this surgeon; but in Dhakhira-yi-Kamilah's book, he introduced himself (8). His teachings and opinions about wounding, surgical procedures, and treatment are reflecting his views that are expressed exactly and certainly and naturally some of them are not correct (6).

Hakim Mohammed, who served as a military surgeon to the Ottoman Empire (1299-1922), collected his surgical experiences in the Dhakhira-yi-Kamilah book, and this book is written in Persian and mainly about the management of wounds and practical techniques (8). Dhakhira-yi-Kamilah includes an introduction, 6 chapters and 30 titles.

At the beginning of this book, the author wrote about general issues, and then he explained more about wounds. It also expressed practical damage and techniques in detail. Hakim Mohamed described the details of the treatment of abdominal and intestinal wounds and suturing of the intestinal hole with ant bite in two different parts of the book (8-10). Dhakhira-yi-Kamilah is of great importance in terms of clarifying the dark corners of medicine in the Safavid Era. This book was written in thirteen years (8,9).

**Wound and suture**

Skin wounds and reducing their recovery time are one of important aspects of medicine (11).

The healing of wound is to reinstate the physical integrity of damaged structures (12). Treatment and care of wounds, increased speed and prevention of infection have always been the attention of physicians. When there is a shear in the body for any reason, they use sutures (13, 14).

Closing wounds with yarn and needles go back thousands of years ago. The remaining writings of ancient Egypt identify that at that time, metal yarns were used for sutures, but these threads had disadvantages such as difficulty in knotting. At the end of the nineteenth century, various materials such as cotton, flax, hemp, silk, animal hair and so on were used to suture and close wounds(13, 14).

## Ants

Insects are one of the most mysterious creatures of creation (15) Ants are among the most diverse creatures on earth and are social insects (16).

There were different opinions about the role of ants in medicine and veterinarians (17).

A number of ants that are capable of biting, stinging and injecting poison into the host body are called stinging ants (18). There are many types of bite ants in the world, and in different areas, there are many species that are known as fire ants (10). The most important aggressive ants, in terms of medicine, are fire ants from the family of Solenopsis (19). Trap-jaw ants use their long lower jaws to disable the prey. When they approach the bait, the lower jaw is opened with an angle of 280° and in this range, they shut their jaw quickly (in less than a millisecond) to crush their prey and hunt the prey (20) (Figure 1 and 2).

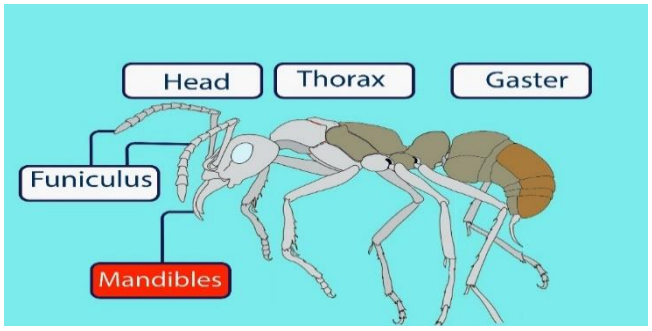


**Figure 1.** An image of the lower jaw of the ant.

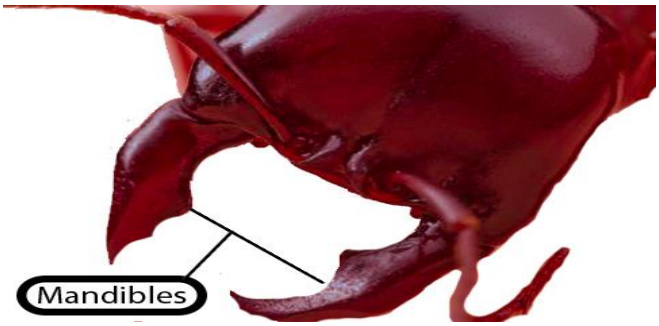


**Figure 2.** An image of the lower jaw of the ant.

## Method of suturing with ants and aftercare

The medical use of the ant existed from the ancient period in a simple way and one of its medical applications in suture was wounds and injuries. In this regard “Angela Royston” says: “Physicians, instead of suturing in surgery, benefited from the jaws of big ants in order to put the corners of the wounds on each other so that they can easily heal the wounds. When the jaws of the live ant are placed on the scar, the ant started to bite (Figure 3), hence the ends of the wounds reached together, then the physician, cut off the body of the ant and separated it from the wound(21) (Figure 4). Susruta, an Indian surgeon around 500 BCE suggested removing foreign material from the wound, then applying large black ants to the wound's edges and separating their bodies from their heads once they had tightly bitten the section with their jaws (22) Ants have been used for centuries to close and suture wounds in Central and South America (23). In Dhakhira-yi-Kamilah's book, Hakim Mohammad has described in particular the surgery of intestinal and abdominal wounds and the suture of the intestinal hole among ant stings (5). Hakim Muhammad used this method to treat wounds and holes in the intestine, and after suturing the intestine with this method, he put it in the abdomen and treated the abdomen, and after putting burned cotton on the wound, he covered it (dressing it up) (8).

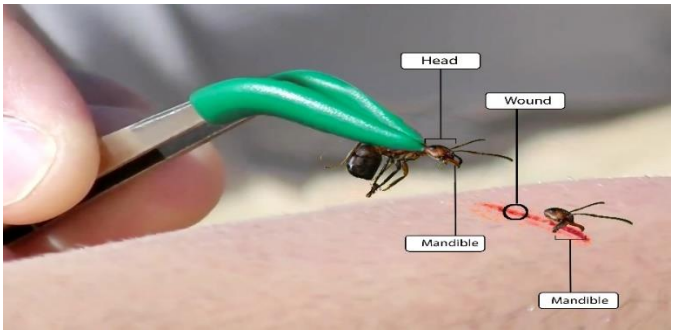


**Figure 3.** How to do suture with ant.

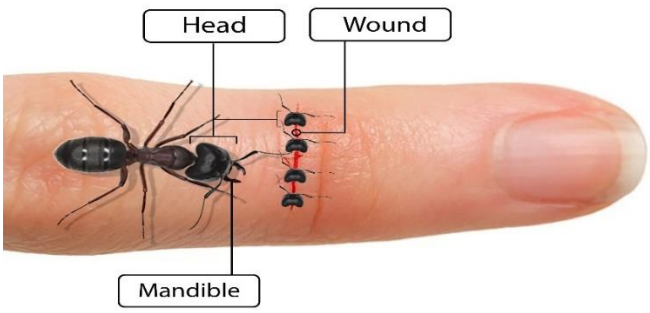


**Figure 4.** The suture was done by ant.

The stings of ants are often painful and with severe itching, and in some cases, with blisters and some other symptoms, and even complications, such as severe sensitivity, anaphylaxis shock and even death(10). In the view of Hakim Mohammad, wound care is that in these patients, the wound is well covered and does not feed (heavy foods) the patient for two days and since three hours after the suture, fatty soup (very light food) must be consumed that is anti-thirst and has nutritious features and do not feed water to the patient to prevent wound infection, and then tamarisk water should be given (boiled water of tamarisk).

the patient should be given this soup for three days and on the fourth day if the patient wants water, he may be given it according to the following method: First, break and ground the pieces of tamarisk and boil in a stone cauldron with water, screen and re-boil to halve and then use.

Among other important points to be considered in these patients is that the patient must be well taken care of and must wear warm clothing. The patient should be barred from having visitors, and if the wound suffered from pus, it should be treated by the following method: olive oil, white wax, turmeric, Onosma dichroanthum Boiss, and washed swamp stone, Chelidonium majus L, washed lentil hematite, and tragacanth; Mix all and put on the wound and remove a few days later. If the patient has pain, resolve the pain in the following way: 45 grams of unripe olive, 13.5 grams of white wax, 18 grams of grounded frankincense, 13.5 grams of alum crystal; make a poultice of them all and add egg oil and put on the scar every day (8).

In addition, many findings indicate that ant treatment and suturing are also effective in preventing infection, which may be due to the ants' chemical defense against infectious agents. The secreted glands are involved in destroying many microorganisms (24).

Nowadays, new and modern methods have been replaced, but sutures with ants are similar to today's sutures, including the following:

- In terms of suture pattern, given that in this method, sutures were individually and in a row. Therefore, it can be known as similar to modern sutures today.

- In terms of absorbability, given that this type of suture was performed in the intestine and intra-abdomen, it seems that it was absorbed and it can be divided into today’s absorbent sutures.

Certainly, the method that Hakim Mohammad introduced in his time and used ants to treat wounds was a very amazing issue and opened a new path in suturing techniques for humanity. But this method had limitations. It was possible to use sutures with ants in certain places such as the intestines and abdomen. Its use in some organs that are hard and cartilaginous is considered one of the limitations of the work. Sometimes, if necessary, to improve the condition of the sutures in the wounds, it was necessary to use the ant several times to create a stronger suture. The killing of ants in this process is also one of the disadvantages of this technique.

Today's medicine is the result of the work and actions of the former times and even events that occurred in the past.

## Conclusions

Suturing is one of these methods. Hakim Mohammed used ant for sutures of abdominal wounds and intestines.

In this paper, suturing method with ant and nutrition method and treatment of pain and after suturing pus by Hakim Mohammad during the Safavid Era was investigated. It is worth mentioning that the present study, based on the latest data of the researchers of this paper, is the first research on suture surgery with ant by Hakim Mohammad, the Iranian physician of the Safavid Era, so there is not much information about Hakim Muhammad and the suture method with ant. Study of the treatment methods of predecessors shows us developments and the path to the progress of surgical affairs and can be used in the direction of further advance.

### Author contribution

**SS** writing, methodology, investigation. **MQ**, investigation, writing. **FK** conceptualization, supervision, writing, investigation.

### Conflict of interest

No potential conflict of interest was reported by the authors.

### Ethical approval

IR.GOUMS.REC.1401.205

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# Explaining the psychological experiences of nurses during the first peak COVID-19 pandemic

Marjan Hosseinnia [1] , Seyed Mohamad Amin Mousavi Shalmaei [2] , Zohreh Salmalian [3], Naema Khodadadi-Hassankiadeh [4]*

[1] School of Pharmacy, Department of Clinical and Administrative Sciences, Notre Dame of Maryland University, Baltimore, Maryland, USA

[2] School of Dentistry, Guilan University of Medical Sciences, Rasht, Iran

[3] Department of Nursing, Langroud School of Nursing and Midwifery, Guilan University of Medical Sciences

[4] Guilan Road Trauma Research Center, Guilan University of Medical Sciences, Rasht, Iran

## Abstract

**Introduction:** The unexpected spread of COVID-19 with high risk of transmission, fear and anxiety, and a load of negative emotions followed for nurses. It is necessary to assess the psychological experiences of nurses during the first peak COVID-19 pandemic.

**Materials and Methods:** In this qualitative study, with the approach of conventional content analysis approach, the participants were selected through proposed-based sampling and snowball from the COVID-19 centers of Guilan province in March 2020. The number of 20 participants with various demographic characteristics (Gender, age ...) entered the study. The tools used were in-depth and semi-structured interviews.

**Results:** Most of the participants were women, married and nurses. Six categories were obtained: not perception, worries, and pretending, horrible observations, pre-psychological symptoms and psychological symptoms.

**Conclusion:** Psychological experiences of nurses in COVID-19 center in Guilan were expressed in a range of not perceptions and worry until the appearance of numerous pre and psychological symptoms. The psychological needs of this group must be considered at all stages of the crisis. Psychological support by mental health workers should be considered in line with the development of the crisis to reduce the stress on nurses.

**Keywords:** Psychological, Stress, Experiences, Nurse, COVID-19

*Corresponding Author: Naema Khodadadi-Hassankiadeh

✉ Email: n_khodadady@yahoo.com

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## Introduction

The COVID-19 is one of the types of the coronavirus family (1, 2). This disease spread rapidly throughout China and other countries of the world and became an emergency of the World Health Organization (W.H.O) (3, 4). China remains the highest-risk region (5, 6). The rapid increase in the number of COVID-19 cases in China in late 2019 reminds us how quickly health systems can be challenged to provide appropriate care (7, 8). COVID-19 is clearly a global health problem, especially for developing countries such as Iran (9, 10).

As COVID-19 is spreading rapidly around the world, it is clear that countries are not prepared to protect healthcare workers, patients, and the public, given the inevitability of a global COVID-19 pandemic. Despite the availability of guidance to prevent the H1N1 pandemic in 2009 and the Ebola outbreak in 2013-2016, it is shocking. A sign of the lack of preparedness is that nurses and other healthcare workers were forced to reuse damaged masks. It was estimated that 3,300 health workers were infected and 22 died in China due to "lack of adequate personal protective equipment (11).

Among all health workers, nurses are playing an extraordinary role in the fight against COVID-19, which quickly became a pandemic. During the pandemic, nurses demonstrated their commitment to their profession and patients by putting in intensive efforts by risking their lives in their respective departments (12). Nursing is the most common healthcare role in the United States (US) and the world (13). Approximately 3.8 million nurses in the US and more than 20 million nurses around the world are working with various occupational stressors (5) Most (68.3%) nurses had high levels of occupational stress(14). Moreover in another study, the results showed that the proportion of low occupational stress was 6.1 %, the proportion of medium occupational stress was 47.1 %, and the proportion of high occupational stress was 46.8 %, all of which were higher than the national standard (15). The unexpected outbreak of COVID-19 with high risk of transmission brought fear and anxiety to nurses (16). Some of the pressures that nurses in Wuhan had were: high risk of infection, insufficient protection against the virus, overwork, frustration, discrimination, isolation, caring for patients with COVID-19 with a burden of negative emotions, lack of contact with family and fatigue. Such dire situations cause mental health problems such as stress, anxiety, depressive symptoms, insomnia, denial, anger and fear. These mental health problems not only affect the attention, understanding, and decision-making ability of treatment workers and the fight against COVID-19, but can even have a lasting effect on their general well-being. Hence, health protection. Therefore, protecting the mental health of these nurses is important to control the epidemic and their long-term health (17, 18).

It is necessary to assess the problems and demands of healthcare providers to create a safer healthcare system for an effective response when natural disasters occur. In addition, it is necessary to develop strategies to protect healthcare providers from severe emotional and psychological stress (19). In a study of the experiences of nurses caring for patients with MERS coronavirus syndrome, several themes emerged: "Going into a dangerous field," "Extreme pressure because of MERS," "The strength that makes me bear it," "Growing as a nurse, "and remaining duties (20). Perception of the mental health response after a public health crisis is important in that it can help medical and nursing staff prepare to respond to a disaster. Perception of the mental health response after a public health emergency may help medical workers and communities manage the public's response to a disaster (17). As the review of the literature shows, there has been no published study in Iran and Guilan that describes the experiences of nurses regarding their psychological symptoms during the COVID-19 pandemic. The need to study in this topic is necessary considering the significant statistics of deaths and infections in Guilan province in the first peak compared to other provinces of the country and the death of a significant number of nursing staff in this province.

## Materials and Methods

### Study design

A conventional content analysis was conducted .The primary participants of this research were nurses with the ability to understand and speak Persian who were willing to participate in the study and express their experiences. The first participant was selected through

purposed-based sampling from the hospitals of the COVID-19 treatment center, and the next participants were selected by snowball. An effort was made to include people with diverse characteristics in terms of gender, age, etc. in the study so that the presence of nurses who have various experiences of nursing care in this crisis will help to maximize diversity and achieve theoretical information richness. According to the need and according to the results of data analysis, the researcher conducted interviews with nurses, head nurses (infectious, emergency and ICU wards...) and supervisors and nursing coaches. The information related to the demographic characteristics of the participants includes age, gender, education level, marriage, and the number of children in table 1 (Table 1).

### Data gathering

In-depth and semi-structured individual interviews were the main tools of data collection, which started with several general and open-ended questions related to the research topic; what were your psychological experiences while caring for COVID-19patients?" (2) What feelings and concerns did you experience during this crisis (3) what psychological symptoms did you experience? The interviews were conducted with WhatsApp according to the nurses' desire and the risk of infection. The duration of the interviews was between 30 and 60 minutes.

### Analysis Plan

Immediately after the first interview, the content of the interview was written down in the participant's own words. The interview was then read several times to gain a general perception. The analysis was performed word by word, line by line, and paragraph by paragraph, and the initial codes were assigned. The codes were categorized according to similarities and differences and placed in initial categories. Code and category naming was revised several times. The ambiguities were clarified by checking the issues with the participants.

### Trustworthiness

The issue of ensuring the trustworthiness of the data is essential for conducting qualitative research. Lincoln and Guba proposed four criteria: credibility, dependability, confirmability, and transferability (21). Participant review was used to ensure the credibility of the data. The participants had the opportunity to correct any misunderstanding in the interviewer's perceptions. In order to gain dependability, experts in qualitative research reviewed the codes and categories. Furthermore, we tried to achieve confirmability. All stages of the research were written in detail so that other researchers could follow the data and possible biases were eliminated.

## Results

Most of the participants were women, married and nurses. The demographic characteristics of the participants in the study are shown in table 1.

**Table 1.** Demographic characters study population.

| No | Gender | Age | Responsibility | Marital | Number of children |
|---|---|---|---|---|---|
| 1 | Male | 54 | Nursing coach | Married | 3 |
| 2 | Male | 53 | Supervisor | Married | 2 |
| 3 | Female | 50 | Head nurse | Married | 2 |
| 4 | Female | 54 | Supervisor | Married | 2 |
| 5 | Female | 52 | Nurse | Married | 2 |
| 6 | Female | 53 | Nurse | Widove | 2 |
| 7 | Female | 54 | Nurse | Married | 2 |
| 8 | Female | 53 | Supervisor | Married | 2 |
| 9 | Female | 52 | Nurse | Married | 2 |
| 10 | Female | 53 | Metron | Married | 1 |
| 11 | Female | 35 | Nurse | Single | 0 |
| 12 | Female | 30 | Nurse | Married | 1 |
| 13 | Female | 32 | Nurse | Single | 0 |
| 14 | Female | 36 | Nurse | Single | 0 |
| 15 | Female | 26 | Nurse | Single | 0 |
| 16 | Female | 29 | Nurse | Single | 0 |
| 17 | Female | 45 | Nurse | Married | 2 |
| 18 | Female | 42 | Nurse | Divorce | 3 |
| 19 | Male | 33 | Nurse | Single | 0 |
| 20 | Female | 54 | Associate Degree | Married | 3 |

There were 6 categories of not perception, worries, and pretending, horrible observations, pre-psychological symptoms and psychological symptoms (Table2).

**Table 2.** Psychological symptoms of nurses during the first peak COVID-19 pandemic.

| Categories | Subcategories |
|---|---|
| A.Not perception | 1. From the authorities |
| | 2. From the wife |
| | 3. From the patient |
| | 4. From uninformed clients |
| | 5. From the people |
| B. Worries | 1. For patients |
| | 2. For being a carrier |
| | 3. For families |
| | 4. For the suffered loved ones |
| | 5. For the people |
| | 6. For yourself |
| | 7. For colleagues |
| | 8. Regarding withdrawal of families |
| | 9. About the officials |
| C. Pretending | 1. Obligation to good appear |
| | 2. Requirement to have a smile |
| | 3. The need to look funny |
| D.Unfortunate observations | 1. Occurrence of human massacre |
| | 2. Death of patients |
| | 3. Occurrence of abnormal behaviors |
| | 4. Occurrence of of anxiety in society |
| | 5. Unpleasant changes |
| E.Pre-psychological symptoms. | 1. Feeling of homesickness |
| | 2. Feeling of fear |
| | 3. Lack of attention to appearance |
| | 4. Feeling of mental fatigue |
| | 5. Ignoring wishes |
| | 6. Worrie about the future |
| | 7. Feeling of not trusting |
| | 8. The feeling of losing peace |
| | 9. Feeling of insecurity |
| F- Psychological symptoms | 1. Feeling of panic |
| | 2. Feeling stressed |
| | 3. Feeling anxiety |
| | 4. Feelings of despair and hopelessness |
| | 5. Crying and moan |
| | 6. Feeling guilty |
| | 7. Praying as the only solution |
| | 8. Feeling depressed |

A. Not perception

1. From the authorities. Participant 1: I am a prolific person, if my husband doesn't come to pick me up in the evening, believe me, I will stay in the hospital for 24 hours... But I feel that no one on the treatment staff understands the amount of work and the strain of working with these patients and the fear of patients takes a lot of energy.

2. From the wife. Participant 14: My husband's sister posted the steps of baking bread at home on WhatsApp, my husband expects me to bake bread for our family. They don't understand me at all.

3. From the patient.

Participant 15: We wear so much, sometimes we don't hear. The patient was calling us and we did not hear and did not go to him. We saw him shouting, are you a deaf nurse?

4. From uninformed clients.

Participant 6: Some people don't really understand, last night a patient came without an ultrasound with a ruptured amniotic sac. I tell you, what does your ultrasound report say, I came from a party. I wanted to hit him. We haven't seen our siblings for a few months, they are having a party. In the end, nothing happens to them, then they say that we all threw a party, but nothing happened.

5. From the people. Participant 10: Nurses work in such conditions, but people easily travel selfishly as much as possible, while they are informed but impatientto stay at home.

B. Worries.

1. For patients. Participant 9: I had seven discharges today, they thanked us so much, and I pray that there will be no problems for them at home. They don't last

as long, meaning it's not as long from the time they're admitted to the time they die, which is a worry.

2. For being a carrier. Participant 12. The situation is really dangerous and everyone is aware of this danger, but my colleagues and I are more concerned about our families than about ourselves. Because we have always been exposed to diseases.

3. For families. Participant 2: My wife's family was very worried and kept asking me on the phone not to go to work at all. Also, my eldest son was very afraid that I would get COVID-19 or maybe bring COVID-19 home.

4. For the suffered loved ones. Participant 2: One of my sisters and also a close friend got COVID-19and I had to take care of COVID-19 patients in the hospital. Outside of working hours, I will also give them advice and injections. Of course, now I have a clear conscience that I was able to manage these situations to some extent.

5. For the people. Participant 20: The situation is very bad, many people are dying, and nothing can be done, nothing.

6. For yourself. Participant 3: One of my employees was very young, her husband had died. At the beginning of the COVID-19 pandemic, her daughter, who was in the fourth grade of school, called me, if my mother gets infected COVID-19, who will take care of me? Finally, her mother got COVID-19. Unfortunately, he has no one, her husband's family are not good people.

7. For colleagues. Participant 16: I did not go to work because of my child. But all my colleagues were going to work during the crisis. After ten days, I called my head nurse and said that I can't stay at home when you are struggling so much, I will come to work... Now, I have a fever and my CRP test is positive.

8. Regarding withdrawal of families. Participant 2: My family distanced themselves from me as if I had leprosy. My sisters, who always trip in my car, now that they know the possibility of being a carrier of the medical staff, are not even willing to ride in my car. So what about my wife and children? Should they leave me too?

9. About the officials.

Participant 7: Our hands are wound, One's heart cries when he sees it, no one cares at all, and our officials are so relaxed. They forget everything quickly. Heart-wrenching.

C. Pretending

1. Obligation to good appear .Participant 17: Whenever my shift was over, I would go to the dressing room to cry alone so that I could calm down a bit and look refreshed when I got home.

2. Requirement to have a smile. Participant 13: Our boss loves taking pictures frequently. He says to smile in the photo to make people happy. How can you smile with ith this mask and glasses,?

3. The need to look funny. Participant 3: I joked with the patients in the ward today. They were sprinkling their coughs everywhere, I told one of them that I will not be discharged until they get better. There is a boss somewhere. I told him that you are going to destroy Rasht, but I am crying at home alone...

D. Unfortunate observations.

1. Occurrence of the human massacre. Participant 4: Last night, two ward servants who had been working all day until the morning were sick early in the morning. People see dancing in the virtual space, but they don't know what human tragedies are happening and people's loved ones are dying one by one.

2. Death of patients. Participant 6: COVID-19 patients die of fear in ICUs. As soon as they heard that they wanted to send them to the ICU, they would get respiratory distress and die sooner.

3. Occurrence of abnormal behaviors. Participant 3: I am constantly counting equipment. I came in the morning and three containers of alcohol were stolen. I have an anti-theft camera but no time to check.

4. Occurrence of anxiety in society. Participant 2: In addition to anxiety and worry in the staff, this state of anxiety was also found in patients and caregivers. In such a way that even with the slightest symptoms of a cold, they went to the emergency departments a hospital.

5. Unpleasant changes. Participant 3: In the beginning, they moved the nurses' wards too many, which was stressful for them. It never occurred to me that was the head of gynecology and obstetrics, was the head of COVID-19 ward.

E. Pre-psychological symptoms.

1- Feeling of homesickness. Participant 3: I miss my parents very much, they both died. Good luck to those who have the shadow of their parents in this crisis.

2. Feeling of fear. Participant 2: When the Ministry of Health confirmed that the COVID-19 ward has spread in Qom and subsequently in other provinces including Guilan, a state of fear and anxiety gradually appeared in the hospital personnel who should be in the first line of patient care, and the day this became known fear and worry increased.

3. Lack of attention to appearance. Participant number 6. I don't have any boredom left, I go to work with a dull look and no make-up.

4. Feeling of mental fatigue. Participant 18: I am very tired, they say this disease is continuing now. Our work is very, very hard, it's like a war, I'm so tired, and I'm crying all the time.

5. Ignoring wishes. Participant 19: Believe me, I also have the right to have many wishes for myself, it would be nice if people stayed at home.

6. Worrie about the future. Participant 3: I don't know, can we work without personal protective equipment one day? Can you be sure that the virus is gone?

7-. Feeling of not trusting. Participant 13: My colleague and I went on strike outside the department and said that we will not go to the department until you give us good protective equipment. We forced them to prepare for us quickly. I will not throw myself into the well with these ropes.

8. The feeling of losing peace. Participant 3: I don't have the courage to hold my children in my arms now, lest I pass the disease on to them. I also lost the peace that is given to me by hugging them. I haven't sat at a dinner table with my children for a long time.

9. Feeling of insecurity. Participant 16: The duty of a COVID-19 nurse is like that of a mine destroyer in the war, who may be exposed to danger and explosions from the sky, in front and behind, as well as from the ground.

F. Psychological symptoms.

1. Feeling of panic. Participant 4: It's really scary if someone has both COVID-19 and another disease, it's really not known what will happen. A 19-year-old girl with GCS 3 is in the ICU, unfortunately, her lungs are completely white. He had appendicitis. The unfortunate is still in the ICU. They said so much that it was COVID-19, they canceled the operation, they brought him to the ward, he was getting cyanotic, and so we sent him to the ICU again.

2. Feeling stressed. Participant 18: We, who worked in difficult situations, understand that these dances are a moment, but it is hard work and stressful day and night. May God help us overcome this crisis.

3. Feeling anxiety. Participant 11: In very difficult conditions, we struggle with constant anxiety of getting sick and dying.

4. Feelings of despair and hopelessness. Participant 13: One gets disappointed. One of our colleagues, who was a member of the operating room staff, helped us during the COVID-19 crisis and served all the patients. He could not do anything for his mother and their mother died today.

5. Crying and moaning. Participant 14: Photo of a nurse from Lahijan Hospital who died today due to COVID-19, I cry. It was the New Year celebration of her wedding, she had gone to Rasht to choose her wedding dress... I am very sad.

6. Feeling is guilty. Participant 5: My job caused my wife's illness, and now she is hospitalized. His job was an architect. It is quite clear that I transferred the illness to her. Apart from the constant suffering of his illness and misery, which I will not forgive myself for my whole life, I cannot bear the look of his family, who look at me like a criminal.

7. Praying as the only solution. Participant 18: If you can not leave the house at all, stay at home, the situation is very bad. Pray for us.

8. Feeling depressed. Participant 14: I'm depressed. My friend and comrade from university, who we were guarding together, we used to joke and reminisce, got COVID-19 virus and died. As quickly and bitterly.

## Discussion

The lack of not perception of categories was the result of assessment of the psychological experiences of nurses at the COVID-19 Center in Guilan province. It was also reported in previous texts that the conflict between work and family becomes a source of stress because a person tries to sacrifice one for the other. Flexible work is associated with less work-family conflict (22). The existence of differences in language, culture and religion between patients and nurses creates obstacles to clear perception and effective communication and creates a negative impact on the health outcomes of patients. Therefore, the need to improve communication between patients and healthcare providers in order to provide safety performance contributes to the higher quality of care and patient satisfaction (23).

Worries were the next category. Nurses have a right to be worried about the health of themselves and their families. Similarly, in one study, a significant level of worry was reported in health workers. These results should encourage public health officials to increase educational efforts to disseminate reliable information about the different types and provide recommendations on receiving a vaccine booster. Further research on methods to reduce health worker worries about emerging types is warranted (24).

The next category was pretending and looking good. The professional mission of nurses taught them to provide health services with maximum honesty and courage. The conflict between fear and conscience is another experience reported by nurses in a previous study. The result will be that in crises, nurses see themselves in danger but try to perform their duties with good quality. Therefore, they experience internal pressure regarding professional ethics (25-27). In this regard, proper support and creating a sense of security can increase the quality of performing this task by nurses (25, 27).

The next category was the unfortunate observations that these nurses had. In the past, the occurrence of symptoms of post-traumatic stress disorder predominantly overwhelmed by intrusive thoughts in these nurses following unfortunate observations and frequent association of these observations in the minds of nurses was previously reported (28, 29).

The next category was the occurrence of pre-psychological symptoms. It was previously reported that 54.5% of nurses and midwives described their lives as worse since the start of COVID-19, 62.4% felt uncertain in this situation, 42.6% wanted psychological support and 11.8% quit from their profession (30). In a study, the proportion of nurses who received psychological counseling during this pandemic was higher than that of doctors (31).

And similarly, in an Iranian study of nurses' experiences in dealing with a crisis, the themes of psychological reactions with characteristics such as fear and depression were identified. Nurses exposed to severe stress are the hidden victims of these crises. These disorders have a significant impact on their performance. Especially situations such as the loss of loved ones and friends, who are among the victims, and with the extent and severity of the incident, it causes mental and emotional confusion for people (32).

The final category was the occurrence of psychological symptoms in these nurses. Psychological experiences were very wide and were observed in nurses of all ages and positions, i.e., it was described in line nurses who were responsible for taking care of a few patients and head nurses who were responsible for taking care of a large number of patients. These experiences were observed even in nurse educators who were not in charge of direct care of COVID-19 patients. Similarly, among nurses caring for MERS, one of the themes revealed was "extreme pressure due to the presence of MERS"(20). Crisis situations and pandemics can cause mental health disorders even in previously healthy people, and severe stress, anger, irritability, insomnia, sleep disturbances, and mood disorders, including symptoms of depression, panic, anxiety and stress (33, 34).

Psychological symptoms were acknowledged by the participants in its various titles, and anxiety was one of the most important and frequent ones. In a similar study, psychological distress among medical staff, especially fear and anxiety, appeared first, and later post-traumatic stress disorder and depression appeared and continued (35). Since psychological symptoms were evident almost from the first weeks of the crisis when the interviews began, it is recommended to start psychological counseling as these crises pass each day and one should not wait for the formation of post-traumatic stress disorder and depression in them and then treat them (36). In previous studies, to address the mental health issues of hospital workers who are exposed to overwork, stress, difficult moral decisions and multiple deaths, along with the fear of contaminating themselves and their families, a special line they have suggested remote psychiatric consultation (37, 38).

One of the limitations of the present study was the lack of sufficient reference articles and sources due to the relative novelty of the subject, especially in the field of qualitative studies. Examining long-term mental disorders, which is one of the limitations of the study, is suggested in the future.

## Conclusions

The psychological experiences of caring nurses in the COVID-19 centers in Guilan were expressed in a range of not perceptions and worries... and until the occurrence of numerous pre and psychological symptoms. The psychological needs of this group should be taken into consideration at all stages of the crisis. Psychological support by mental health workers should be considered along with the development of the crisis to reduce the psychological pressure of nurses..

### Author contribution

**MH** and **NKH** participated in the research design, content analysis and writing the first draft; **SMAMS**, and **ZS** participated in the performance of the interviews and content analysis; All authors reviewed and confirmed the final manuscript.

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### Conflict of interest

There are no potential conflicts of interest.

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