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Original Article

Association Between Known Close Contact History and Severity of COVID-19 Pneumonia: A Preliminary Evidence Supporting Importance of Filiation

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Abstract

OBJECTIVE: The role of a known contact history in coronavirus disease 2019 severity in secondary cases is unknown. The study was aimed to investigate the relationship between the close contact history and the severity of the disease in coronavirus disease 2019 pneumonia.

MATERIAL AND METHODS: Hospitalized patients diagnosed with coronavirus disease 2019 pneumonia were included. The demographic, clinical, and laboratory data of the patients were collected retrospectively and patients with or without close contact history were analyzed with respect to the severity of pneumonia.

RESULTS: In a total of 100 patients with coronavirus disease 2019 pneumonia, 54 (54%) were male and mean age was 42.28 ± 17.13 years. Respiratory rate/min (P = .033) was higher, duration of hospitalization (P = .043) was longer, need for oxygen therapy (P < .001), intensive care unit admission (P = .001), and severe pneumonia (P < .001) were higher in the group without a close contact history (n = 50). Male gender (OR, 4.77; 95% CI, 1.06-21.32; P = .041), not having a close contact history (OR, 4.03; 95% CI, 1.00-16.13; P = .049), non-hospital-associated patients (OR, 9.59; 95% CI, 1.47-62.41; P = .018), and dyspnea (OR, 7.58; 95% CI, 1.64-34.93; P = .009) were found to be risk factors for severe pneumonia.

CONCLUSION: Known close contact history was associated with non-severe pneumonia and was found to be an independent predictor of disease severity in coronavirus disease 2019 pneumonia. The study provides evidence that filiation may prevent severe disease.

KEYWORDS: Contact with infected person, COVID-19 pneumonia, filiation method, severity of disease
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INTRODUCTION

The coronavirus disease 2019 (COVID-19) caused by the new type of coronavirus (severe acute respiratory syndrome coronavirus-2) infection was first reported in Wuhan, China, in December 2019. Coronavirus disease 2019 declared as a Public Health Emergency of International Concern by the World Health Organization (WHO) is an epidemic public health problem that is primarily transmitted from person to person via droplet and/or close contact with an infected person.[1] Total number of new and serious cases are increasing day by day due to the easy transmission of the virus and substantial spread worldwide since January 2020.

While the total number of cases in the world is over 5 million and the number of deaths is over 340 000, these numbers exceed 150 000 and 4000 in our country, respectively.[2] According to WHO data, in March 2020, the death rate all around the world was 3.4% whereas this rate was reported as 2.3% in our country. For this reason, WHO has reported individual and public isolation and precautionary suggestions, and many countries make intense efforts against the epidemic by various methods.[3] The isolation and determination of close contacts applied to control the infectious circle are an important part of efforts to control infectious disease outbreaks. The contact tracking of transmission chain with detailed contact history to identify the source of infection named as "filiation method" is a widely used method in our country. The filiation method entails screening the chain of contact of the infectious disease, reaching people who got infected by the coronavirus, monitoring them, and isolating the diagnosed patients for treatment. However, for COVID-19, even though there are contradictions as to whether these methods have been successful in outbreak control, Helliwell et al[4] reported in their studies that effective contact monitoring will contribute to the reduction of the overall size of the outbreak and its long-term control. This filiation method, which is based on a close contact history in our country, where the mortality rate is lower than in the world, raises interest in that it can be effective in dealing with the epidemic. However, there is not yet sufficient information about to which degree the secondary cases in the continuation of the transmission chain in close contact with the COVID-19 confirmed cases get through the disease. In many studies to date, the relationship between clinical and laboratory factors and disease severity in COVID-19 pneumonia has been described. Mainly, accompanying chronic

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heart and respiratory diseases, advanced age, male gender, obesity, low oxygen saturation, high respiratory rate (RR), the presence of radiologic abnormalities, elevated serum ferritin, C-reactive protein (CRP), D-dimer, troponin, lactate dehydrogenase, creatinin kinase level, and lymphopenia have been demonstrated to be associated with the severity of the disease and mortality by previous studies.[5,6] However, the role of close contact with the infected individual on the severity of the disease is unknown. Knowing the presence of a close contact will not only prevent the spreading of the virus but will also provide evidence whether individuals with a close contact history will suffer from more severe or milder disease if they become infected, thereby providing preliminary information about the effect of the contact history-based filiation method on disease severity and mortality. In the present study, our aim was to investigate the relationship between contact history and disease severity in patients with COVID-19 pneumonia.

MATERIAL AND METHODS

This single-center retrospective cohort study was conducted during second and last weeks of April 2020 in a tertiary care center.

The study was approved by the local ethics committee of Hacettepe Hospital. (Decision no. 2020/11-04, date: June 9, 2020). Ethical approval was in accordance with the Declaration of Helsinki. The committee from whom the ethical approval was received did not deem the patient's informed consent necessary since the study was retrospective design.

Patients

One hundred adult patients (>18 years) diagnosed with COVID-19 pneumonia who were confirmed by thorax computed tomography (CT) and hospitalized during the study period were analyzed in 2 groups: patients with close contact and patients without close contact history. Close contact was defined as having close (within 1 m) and prolonged (≥15 minutes) contact with the COVID-19 patient. The diagnosis of COVID-19 was based on positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) in obtained samples via nasopharyngeal smears according to COVID-19 guidelines of WHO.[7] According to the model of the National Health Commission, COVID-19 pneumonia was classified as severe and non-severe. The presence of pneumonia was confirmed with CT of the thorax in all cases. Severe pneumonia was defined as RR ≥ 30 breaths/min, resting oxygen saturation <90%, and the presence of at least one of the negative prognostic factors in blood tests at admission: lymphocyte counts $<0.8 \times 10^9$/L, CRP >4 mg/dL, ferritin >500 μg/L, or D-dimer >1 μg/L.[8]

In the study, the healthcare staff and patients who had been hospitalized for reasons other than COVID-19 and infected at the time of hospitalization period were defined as hospital-associated patients, while the rest, in other words, patients coming from outside the hospital, were defined as non-hospital-associated patients.

DATA

Clinical, radiological, and laboratory data were collected from the hospital database and patients' files. The patients' close contact history, symptoms at admission, duration of symptoms (days) before admission, demographics (age, gender, and body mass index), comorbidities, laboratory data including complete blood cell counts, CRP, procalcitonin, ferritin, D-dimer, fibrinogen, cardiac troponin, and baseline blood biochemistry at admission, intensive care unit (ICU) admission, duration of hospitalization, and need for supplemental oxygen therapy were recorded. The data obtained were compared between patients with and without close contact.

Statistical Analysis

The data were analyzed using Statistical Package for the Social Sciences software for Windows v.23.0 (IBM, Chicago, Ill, USA).[9] The normality of variables was examined with Shapiro–Wilk test, boxplots, and Q-Q plots. Descriptive statistics were shown as the mean and standard deviation for normally distributed variables, while median, 25th, and 75th percentiles for normality assumption were not satisfied. For independent continuous variables, 2 groups were compared with independent samples' *t*-test or Mann–Whitney *U* test based on normality assumption for continuous variables. Categorical variables were compared with the chi-square test. The variables which were significant in the comparison of severe and non-severe pneumonia were chosen as variables for multiple logistic regression. Backward elimination was performed with those variables. The results of final logistic regression models were represented with odds ratio (OR), 95% CI, and *P*-value. The level of statistical significance was set at *P*-value < .05. All reported *P*-values were 2-sided.

RESULTS

A total of 100 patients were enrolled and patients were divided into 2 groups: with close contact history (50%, n = 50)

MAIN POINTS

- Early detection of contact history for the control of an epidemic is one of the most important measures to prevent the spread of the virus among the population. Contact tracking based on the close contact history is an effective method of controlling the coronavirus disease 2019 (COVID-19) outbreak.
- Many clinical and laboratory factors that determine disease severity have been identified, confirming that COVID-19 pneumonia can result in serious outcomes. However, the role of a known contact history in disease severity in individuals following the transmission chain is unknown.
- The study investigated the direct association of known close contact history with the severity of the disease in secondary cases with COVID-19 pneumonia which has important implications.
- The evidence highlights that contact detection and contact tracking, in other words, filiation method, play an important role in the course of the disease in secondary cases.
- Gender, whether patients are from the hospital or community, and symptom presentation are also determinative of the severity of COVID-19 pneumonia.

and those without (50%, n = 50) (Figure 1). Fifty-four percent of all participants were male (n = 54) and the mean age was 42.2 ± 17 years (range: 22-92 years). Patients with 2 or more comorbidities were 64.8% (n = 35), most common comorbidities were hypertension (20%, n = 20), diabetes mellitus (13%, n = 13), malignancy (11%, n = 11), asthma (6%, n = 6), chronic obstructive pulmonary disease (5%, n = 5), and systemic diseases, respectively. Of all the patients, 89% (n = 89) were symptomatic. The most common symptoms were dry cough (50%, n = 50), fever (50%, n = 50), fatigue (38%, n = 38), and myalgia (34%, n = 34). Those with severe pneumonia accounted for 28% (n = 28) of the patients, 93% (n = 26) of whom were admitted to ICU, and 23% (n = 6) of them died (Table 1). Table 1 summarizes the demographic and clinical characteristics of the study groups. Demographics, symptom presentation, high fever during hospitalization, symptom duration before admission, and mortality were similar between both groups. Compared to unknown close contact history, RR/min at admission (P = .033) was lower and the length of hospital stay (P = .043) was shorter in patients with close contact history; those who received oxygen therapy (P < .001), who were admitted to ICU (P = .001), and had severe pneumonia (P < .001) were significantly higher in the group without close contact history. Number of hospital-associated patients was more in the group with close contact than without (P = .036).

Laboratory data of the study patients are summarized in Table 2. White blood cell (WBC) and neutrophil counts, CRP, procalcitonin, ferritin, total bilirubin, d-dimer, fibrinogen, and troponin levels were significantly higher and albumin levels were lower in patients without close contact history (WBC; P = .002, neutrophil counts; P = .001, CRP; P < .001, procalcitonin; P = .005, ferritin; P = .006, total bilirubin; P = .003, d-dimer; P < .001, fibrinogen; P = .001, troponin; P P = .005, and albumin; P = .017, respectively). Other laboratory parameters were similar between both the groups. According to multivariate logistic regression analysis, male gender (OR, 4.77; 95% CI, 1.06-21.32; P = .041), patients without close contact history (OR, 4.03; 95% CI, 1.00-16.13; P = .049), non-hospital-associated patients (OR, 9.59; 95% CI, 1.47-62.41; P = .018), and the presence of dyspnea at admission (OR, 7.58; 95% CI, 1.64-34.93; P = .009) were found to be risk factors for severe pneumonia (Table 3).

DISCUSSION

The primary finding of the study was that known close contact history with an infected person was associated with non-severe pneumonia and was found to be an independent predictor of the severity of COVID-19 disease. This study is the first to investigate the direct association of close contact history with the severity of the disease in patients with COVID-19 pneumonia. Contact tracking based on the close contact history is an effective method of controlling the COVID-19 outbreak. Recently, Halliwel et al[4] evaluated the isolation and contact tracking ability to control outbreaks using a mathematical model through scenarios representing potential transmission properties. The results of their study emphasized that effective contact monitoring and isolation will be effective in shrinking the epidemic size and controlling it for a longer period of time, but additional interventions are needed. In another epidemiological study investigating the effect of close contact, contact detection and contact tracking were reported to reduce the time during which cases are contagious and reproductive number (R).[10] The countries such as China, the Republic of Korea, Singapore, and including our country have tightly monitored contact and applied quarantine measures to ensure stabilization of the epidemic.[11,12] Since the first weeks of the epidemic, Turkey has applied extensive contact monitoring and isolation measures with a wide range of teams and has managed to lag behind many countries in the number of cases and mortality rates. Our study was conducted in a tertiary care center located in the third biggest and capital city of the country with the highest number of diagnosed cases. Although the study population

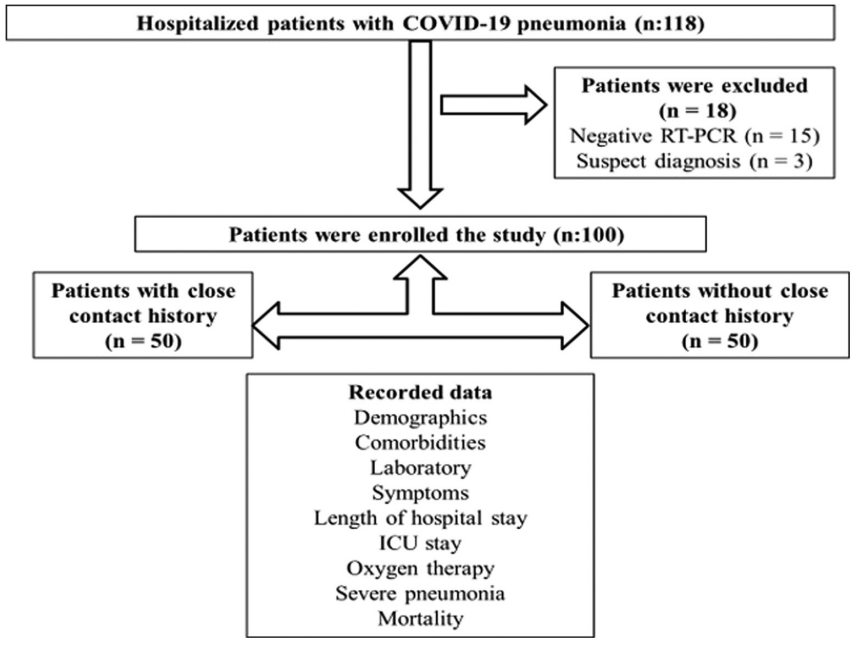

Figure 1. Flow chart of the study.

Table 1. Demographics and Clinical Characteristics of the Patients

	All Patients n = 100	Patients with Close Contact n = 50	Patients Without Close Contact n = 50	*P*
Age*	42.28 ± 17.13	45.08 ± 16.39	51.48 ± 17.42	.062
Gender***				
Male	54 (54)	24 (48)	30 (60)	.229
BMI*	26.31 ± 4.03	25.91 ± 3.56	26.71 ± 4.45	.319
Smoking history***	32 (33.7)	16 (32.7)	16 (34.8)	.826
Active smokers***	3 (11.1)	1 (7.7)	2 (14.3)	.586
Comorbidity***	54 (54)	25 (25)	29 (58)	.422
<2	19 (35.2)	12 (48)	7 (24.1)	.067
≥2	35 (64.8)	13 (52)	22 (75.9)	
Symptom presentation***	89 (89)	46 (92)	43 (86)	
Asymptomatic	11 (11)	4 (8)	7 (14)	.338
Dry cough	50 (50)	27 (54)	23 (46)	.424
Fever	50 (50)	23 (46)	27 (54)	.424
Fatigue	38 (38)	22 (44)	16 (32)	.216
Myalgia	34 (34)	20 (40)	14 (28)	.205
Dyspnea	25 (25)	10 (20)	15 (30)	.248
Sore throat	20 (20)	12 (24)	8 (16)	.317
Diarrhea	11 (11)	8 (16)	3 (6)	.110
Headache	10 (10)	5 (10)	5 (10)	1
Sputum production	10 (10)	5 (10)	5 (10)	1
Chest pain	7 (7)	3 (6)	4 (8)	.695
Anosmia	6 (6)	5 (10)	1 (2)	.092
Runny nose	6 (6)	3 (6)	3 (6)	1
Conjuctivitis	2 (2)	1 (2)	1 (2)	1
Hemoptysis	2 (2)	0	2 (4)	.153
Respiratory rate/min at admisson*	21.17 ± 4.21	20.03 ± 4.05	22.19 ± 4.13	**0.033**
High fever during follow-up***	25 (25)	9 (18)	16 (32)	.106
Oxygen therapy***	28 (28)	6 (12)	22 (44)	**<.001**
Symptom duration before admission (day)**	4 (1-7)	3 (1.5-7)	4 (1.5-7)	.667
Hospital-associated patients***	36 (36)	23 (46)	13 (26)	**.036**
Length of hospital stay (day)**	7 (3-12)	7 (3.5-12)	10 (6.5-21.5)	**.043**
ICU stay***	26 (26)	6 (12)	20 (40)	**.001**
Severe pneumonia***	28 (28)	6 (12)	22 (44)	**<.001**
Death***	6 (6)	3 (6)	3 (6)	1

*Mean ± SD; **median (IQR); ***n (%).
BMI, body mass index, ICU, intensive care unit.
For *P* values with a numeric value less than 0.05, a bold letter was used because it indicates statistical significance.

has been evaluated by contact history inquiry regardless of the filiation records, our results are a pre-registration that reflects the outputs of this method, as it should be based on a common logic with the filiation method. Although it has been known that control of the epidemic could be provided by detection of contact history, its effect on the course of the disease in the detected cases (secondary cases) is unknown. As far as we know, only the relevant parameters were examined in research by Tian et al.[13] and it was found that those with a history of known close contact did not differ according to the severity of the disease. In their study, the number of included patients was higher than our study, but COVID-19 suspicious cases and patients without pneumonia were also included, and definitions for severe and non-severe cases were based on symptoms and not the laboratory results. In our study, all included patients had the diagnosis of pneumonia confirmed by CT of the thorax, suspicious cases were not included, and severe and non-severe pneumonia definitions

Table 2. Selected Laboratory Parameters of Enrolled Patients

	Normal Range	All Patients n = 100	Patients with Close Contact n = 50	Patients Without Close Contact n = 50	*P*
WBC count (×10⁹/L)*	4.1-11.2	5.95 ± 3.15	5 ± 2.12	6.91 ± 3.7	**.002**
Neutrophil count (×10⁹/L)*	1.8-6.4	4.11 ± 2.72	3.22 ± 1.86	5 ± 3.15	**.001**
Lymphocyte count (×10⁹/L)*	1.2-3.6	1.29 ± 0.65	1.29 ± 0.56	1.29 ± 0.74	.966
Platelet count (×10⁹/L)*	159-388	184 ± 67	189 ± 58	178 ± 75	.419
Hemoglobin (gr/dL)*	11.7-15.5	13.33 ± 2.07	13.4 ± 1.9	13.22 ± 2.25	.727
CRP (mg/dL)**	0-0.8	1.26 (0.51-3.69)	1.13 (0.57-2.51)	3.72 (1.43-12.8)	**<.001**
Procalcitonin (ng/mL)**	0-0.1	0.04 (0.02-0.06)	0.04 (0.02-0.05)	0.06 (0.04-0.16)	**.005**
Ferritin (µg/L)**	11-307	81.75 (40-311.2)	69.4 (39.6-331.8)	232 (72-504.1)	**.006**
AST (U/L)**	<35	24 (20-33)	27 (22.5-32)	29 (22-46.5)	.121
ALT (U/L)**	<35	20 (15-30)	21 (15.5-35.5)	26 (17-32.5)	.060
Total bilirubin (mg/dL)**	0.3-1.2	0.5 (0.39-0.72)	0.46 (0.4-0.6)	0.68 (0.47-0.88)	**.003**
Albumin (g/dL)**	3.5-5.2	3.95 (3.6-4.21)	4.06 (3.75-4.27)	3.73 (3.05-4.15)	**.017**
LDH (U/L)**	<247	185 (159-247)	211 (152-258)	218 (182-370)	.088
Sodium (mEq/L)*	136-146	136 ± 3.3	137 ± 2.7	136 ± 3.76	.091
Potassium (mEq/L)*	3.5-5.1	4.06 ± 0.49	4.02 ± 0.36	4.1 ± 0.6	.442
Creatine kinaz (U/L)**	<145	83 (53-164)	106 (55-188)	76 (39.5-136)	.401
D-dimer (µg/L)**	0-0.55	0.44 (0.25-0.96)	0.4 (0.25-0.77)	0.88 (0.43-1.88)	**<.001**
Fibrinogen (mg/dL)*	180-350	413 ± 151	364 ± 101	460 ± 175	**.001**
Troponin (ng/L)**	8.4-18.3	3.6 (2.3-5.8)	3.6 (2.3-5.3)	4.6 (2.4-14.5)	**.005**

*mean ± SD; **median (IQR).
SD, standard deviation; WBC, white blood cell; CRP, C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen.
For *P* values with a numeric value less than 0.05, a bold letter was used because it indicates statistical significance.

were based on clinical, laboratory, and radiological evaluations which strengthen the accuracy of our results. Although the relationship of the known close contact history with the mild course of the disease may suggest that it may be due to early reference, surprisingly our results showed that the duration of symptoms before admission did not differ between those with and without a history of close contact. However, knowing the contact suggests that it will force the individual to take more precautionary behavior, such as considering the number of contact with the index cases and its duration, so that viral transmission and viral load may be less. In the study of Liu et al[14], where they examined viral RNA shedding patterns in mild and severe COVID-19 patients, they found that the average viral load of severe cases was 60 times higher than mild cases. In the study, they reported that viral load would be a useful marker for disease severity and prognosis. In addition, it has been demonstrated that the transmission dynamics of COVID-19, such as the type of contact, the contact area (household, etc.), in which period of the disease was the contact occurred (especially in the first week of the disease and in the pre-symptomatic period), affects the contagiousness.[15] We found that the hospital-associated patients in our study were higher in the non-severe group and the non-hospital-associated patients increased the severity of the disease almost 10 times. This supports our estimation that even if pneumonia develops in secondary cases after contact in environments where contact control is provided in organized and under controlled conditions, the course of the disease is milder and this is due to the fact that the viral load in transmission may have been low. However, the study by Wander et al[16] has suggested that the exposure to the virus from high-viral load sites, for example, stool, should be evaluated as a risk factor for severe COVID-19-related illness in

Table 3. Factors Associated with Severe Pneumonia Among Patients with COVID-19: Multivariate Model

Risk Factors	Odds Ratio	95% CI	*P*
Age	1.02	0.98-1.07	.257
Male gender	4.77	1.06-21.32	**.041**
Patients without close contact	4.03	1.00-16.13	**.049**
Non-hospital-associated patients	9.59	1.47-62.41	**.018**
Symptom duration before admission	1.07	0.91-1.26	.384
Dyspnea	7.58	1.64-34.93	**.009**

For *P* values with a numeric value less than 0.05, a bold letter was used because it indicates statistical significance.

healthcare workers. While the proportion of healthcare workers with severe illness in China was 45%, the rate decreased to 9% after a month.[17] It has been suggested that this decline was achieved by providing adequate personal protective equipment to healthcare workers in the hospital and adopting the importance of protection with training programs. In our center, personal protective equipment was provided to healthcare workers and all healthcare staff had received the necessary training before the study period. However, our inference remains as an assumption as we cannot evaluate other factors affecting viral load and contagiousness. Although it is attempted to prevent secondary transition with the filiation of an infected individual, many authors point out that 44-62% of secondary cases were transmitted by transmission in the pre-symptomatic period of index cases and noted the significant deficit of the filiation method.[18,19]

In the previous studies, many clinical and laboratory features that determine disease severity have been identified, confirming that COVID pneumonia can result in serious or even fatal outcomes.[20-22] The demographic and clinical factors such as older age, male sex, comorbidities, obesity, smoking, and symptom presentation have been demonstrated to be associated with the severity of the disease.[20] In our study, there were no confounder factors in terms of evaluation of disease severity, since those with and without contact history had similar characteristics in terms of demographics and symptoms. A multi-center study by Feng et al[20] demonstrated that length of hospital stay, oxygen therapy, increased inflammatory indicators, such as WBC, neutrophil count, CRP, and procalcitonin, and decreased acute phase reactant such as albumin were associated with the severity of the disease. Also, hematological, coagulative, and sepsis-related laboratory abnormalities, including increased D-dimer, fibrinogen, total bilirubin, and troponin, have been reported to be associated with the disease severity in COVID-19.[21] Especially in cases with sepsis, dyspnea was characterized by the need for supplemental oxygen, increased RR, increase in bilirubin, and severe respiratory symptoms, and these parameters were associated with the severity of the disease.[20,22]

In our study, we showed that severe pneumonia was associated with non-close contact history. Likewise, the results of clinical and laboratory severity predictors, including WBC, neutrophil, CRP, procalcitonin, albumin, total bilirubin, ferritin, D-dimer, fibrinogen, RR, oxygen therapy, were associated with these cases. In a study by Li et al.[23] it was shown that dyspnea was related to the severe damage to alveoli in severe pneumonia cases. In many studies, male dominance has been reported in COVID-19 cases, and in some, it has been shown that male sex was associated with refractory disease and death at a fatality rate of 1.1-2.8%.[24,25] Similar to previous reports, our results demonstrated that dyspnea was associated with a risk of 7.58-fold increase, and male was associated with a risk of 4.77-fold increase in severe pneumonia.

One of the important limitations of the study was that the factors related to the viral load that patients were exposed to and the other possible individual contact that might affect the contagiousness could not be evaluated due to the retrospective nature of the study.

In conclusion, the present study showed that the known close contact history with an infected person was associated with non-severe pneumonia and found to be an independent predictor of the severity of the disease. Male sex, non-hospital-associated patients, and dyspnea at presentation were also independent risk factors associated with severe pneumonia in patients with COVID-19. Our study suggests the evidence that contact detection and contact tracking, in other words, filiation method, plays an important role in the course of the disease in secondary cases. One of the reasons for the lower mortality rate seen in our country may be successful filiation.

Ethics Committee Approval: This study was approved by Ethics committee of Hacettepe University, (Approval No: 2020/11-04).

Informed Consent: Informed consent is not necessary due to the retrospective nature of this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Concept – İ.I., M.G.İ.; Supervision – İ.I., M.G.İ., F.T.; Resources – İ.I., E.D.; Materials – İ.I., M.G.İ., F.T.; Data Collection and/or Processing – İ.I., M.G.İ., F.T.; Analysis and/or Interpretation – İ.I., M.G.İ., F.T., E.D.; Literature Search – İ.I.; Writing Manuscript – İ.I., E.D.; Critical Review –İ.I., E.D.

Declaration of Interests: The authors have no conflict of interest to declare.

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