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Short Communication

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Outcomes of COVID-19 Among High-Risk Individuals: A Study Comparing Febrile and Afebrile Presentation

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Abstract

Background: Fever is one of the most frequent symptoms of coronavirus disease 2019 (COVID-19) and clinicians are faced with a practice question on whether fever is a risk for progression of disease especially in persons with risk factors for severe illness. We studied if a difference exists in the clinical course and outcome between febrile and afebrile (symptomatic) presentation.

Methods: Patients aged > 18 years with confirmed COVID-19 with at least one risk factor for severe illness were studied. Enrolment was done from a home COVID-19 care cohort between May 2020 and March 2022. Participants were divided into febrile and afebrile groups and further divided into six sub-groups based on their comorbidities (diabetes mellitus, hypertension, chronic lung disease, chronic kidney disease, liver disease and others) using a pre-specified inclusion method. Severity of illness was classified as non-hypoxic or hypoxic and clinical course was monitored.

Results: A total of 3,752 patients were studied, of whom 965 (25.7%) had severe illness and 117 (3.1%) died. Persons with obesity ($P < 0.001$), chronic kidney disease ($P = 0.003$) and chronic liver disease ($P = 0.02$) more frequently had presentation without fever. No significant difference in hypoxia ($P = 0.35$) or mortality ($P = 0.50$) was observed between febrile (n = 1,240) and afebrile (n = 2,512) presentation.

Conclusion: Fever in COVID-19 was not associated with severe illness or mortality. The overall and risk factor specific mortality observed in our study is substantially low, probably due to lesser bias in selection of study participants or due to ethnicity of study population.

Keywords: Coronavirus disease 2019; Severe acute respiratory syndrome coronavirus 2; Diabetes mellitus; Hypertension; Chronic lung disease; Chronic kidney disease; Chronic liver disease

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Introduction

Fever is the most frequent symptom in symptomatic coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) identified in the Wuhan province of China in December 2019 [1]. The clinical course of acute illness has two phases, spanning over 2 weeks [2]. The first week of illness is characterized by fever, myalgia, sore throat, running nose, cough, headache, dysosmia and loose stools with a normal oxygenation status in most individuals. The second week is the critical week, when infected persons may either recover or may develop worsening of cough, breathlessness and symptomatic or asymptomatic hypoxia [2]. While most infections are asymptomatic, symptomatic presentation can be febrile or afebrile. It is unclear if there is a difference in the clinical course between febrile and afebrile (but symptomatic) COVID-19.

High risk for severe COVID-19 includes advanced age, diabetes mellitus (DM), hypertension (HT), chronic lung disease (CLD), chronic kidney disease (CKD), chronic liver disease (CLiD), cardiovascular disease (CVD), cancer, human immunodeficiency virus (HIV), neurological disorders, obesity, pregnancy and conditions requiring corticosteroid or immunosuppressive medications [3]. Studies have combined the presenting symptoms in patients with risk factors for severe illness and observed a fever prevalence of 72-98.6% [4, 5]. A review of 102 studies found hypertension (28.3%) as the most prevalent risk factor followed by DM (14.2%), CVD (12.3%) and CKD (5.1%) with an observed mortality of 8.9% (confidence interval (CI): 6.1 - 11.8) [6]. However, there is lack of studies informing the difference in presenting symptoms between patients with specific co-morbidities and their outcome.

This study observed if a difference exists in the clinical course of COVID-19 between febrile and afebrile (symptomatic) presentation and if there are any meaningful differences in outcomes between individuals having different prior chronic medical illness.

Materials and Methods

Study setting and sample

We studied 3,752 consenting patients aged > 18 years resid-

ing in Chennai and its suburbs (Thiruvallur, Chengalpattu and Kancheepuram) diagnosed with RT-PCR of nasopharyngeal swab confirmed COVID-19 between May 2021 and March 2022 who had at least one risk factor for severe illness. Ethics Committee of Society for Humanism Education and Development, Chennai and Institutional Ethics Committee of Sri Ramachandra Institute of Higher Education and Research, Chennai approved the study. Enrolment was done from the home COVID-19 care cohort of Society of Humanism Education and Development using a consecutive sampling method and from Sri Ramachandra Medical College and Research Institute using a convenient sampling method. Patients who were not able to narrate their clinical history were excluded. Upon enrolment one of the authors obtained information on symptoms related to COVID-19. Study participants were followed for new onset symptoms or resolution of symptoms till day 14 from the onset of the first symptom attributable to COVID-19. Patients were included in the fever group based on self-reporting of fever by patient or their care taker. Presence of chronic medical illness (DM, HT, CLD, CLiD, CKD, cancer, HIV and immune-mediated diseases) was ascertained by clinical history and perusal of health records and details of current medications. Obesity was defined as body mass index (BMI) ≥ 30 kg/m^2.

Categorization and observation

For the purpose of assessing if the type of symptom differed based on risk factor, we divided participants into five groups based on their comorbidities as: a) DM group (inclusive of additional chronic medical illness); b) HT (without DM, inclusive of additional chronic medical illness); c) CLD (exclusive of DM and HT); d) CKD (exclusive of DM and inclusive of HT); e) CLiD (exclusive of DM and HT); and f) others (obesity, malignancy, HIV, autoimmune diseases, on chronic immunosuppression due to other reasons; exclusive of DM and HT). The DM group was allowed to include all additional risk factors; HT group was allowed to include all non-diabetic risk factors and CKD group had non-diabetic hypertensives. All other groups were exclusive of DM and HT. This method permitted some homogeneity in the non-diabetic groups.

The severity of COVID-19 was classified as non-hypoxic or hypoxic (when peripheral oxygen saturation was $\leq 95\%$). The clinical course of non-hospitalized participants was monitored till day 14 of illness through daily telephonic call or visit by community health worker and those hospitalized were monitored till 28 days from onset of symptoms or till hospital discharge (whichever is longer). Daily oxygenation status and details of oxygen therapy were obtained. Complete details of tests and treatment administered to patients were not obtained.

Analysis

Differences in age, gender, symptoms, risk factor for severe illness, severity of illness and mortality between the febrile and afebrile groups overall and within the five sub-groups were analyzed with Chi-square test, Fisher's exact test, unpaired *t*-test and Mann-Whitney U test as appropriate. A P value < 0.05 was interpreted as statistically significant. Graph Pad Prism version 9.2.0 was used for analysis.

Results

Comparison of symptoms

We studied 3,752 patients with at least one risk factor for severe COVID-19. Patients with obesity ($P < 0.001$), CKD ($P = 0.003$) and CLiD ($P = 0.02$) more frequently had presentation without fever. No significant difference in frequency of fever was observed in persons with other risk factors. Patients without fever got tested significantly late compared to those with fever. Table 1 explains the baseline characteristics of study participants classified as those experiencing fever and those with non-febrile symptoms. Table 2 explains the comparison of symptoms in the study sub-groups. The additional chronic medical illnesses in the DM group were HT (n = 656), CKD (n = 170), lung disease (n = 70), liver disease (n = 44), obesity (n = 404), neurological disorder (n = 73), coronary heart disease (n = 305), and HIV (n = 12) on immunosuppressants (n = 10). Additional chronic medical illnesses in HT group were lung disease (n = 34), CKD (n = 34), liver disease (n = 10), obesity (n = 53), HIV (n = 14) and immunosuppressant intake (n = 12). Most (293 out of 339) in CKD group had additional HT.

Outcomes

Nine hundred and sixty-five (25.7%) had severe illness and 117 (3.1%) died. The study observed no significant difference in hypoxia between the febrile and afebrile groups ($P = 0.35$); however, participants with CLD having febrile presentation had significantly higher prevalence of hypoxia ($P = 0.03$). CKD group had the highest mortality. There was no mortality difference ($P = 0.50$) between febrile and afebrile presentation.

Discussion

Our study appears to be the first study which compared severity of illness and mortality due to COVID-19 based on presence or absence of fever as a presenting symptom. High fever is one of the concerning symptoms among COVID-19 patients and can persist till 7 days [4]. Clinicians are faced with a practice question on whether fever is a risk for progression of disease, especially in persons with risk factors for severe illness. Our study observation indicates that presence of fever is neither a risk factor for severe disease nor mortality among patients with at least one risk factor for severe illness. This observation is likely to be reassuring for patients and family practice clinicians initially evaluating suspected and confirmed COVID-19 patients with fever.

Consistent with many published meta-analyses, our study observed that HT was followed by DM as the most frequent

Table 1. Comparison of Symptoms and Severity of Illness Between Febrile and Afebrile Symptomatic Groups

Parameter	Febrile group (n = 1,240), mean ± SD or no. (%)	Afebrile symptomatic group (n = 2,512), mean ± SD or no. (%)	P value
Age, years	42.4 ± 38.6	52 ± 22.9	< 0.0001
Gender			
Male	841 (67.8)	1,461 (58.1)	< 0.0001
Female	399 (32.1)	1,051 (41.8)	< 0.0001
Prior chronic medical illness			
Diabetes mellitus	443 (35.7)	921 (36.6)	0.57
Hypertension	516 (41.2)	978 (38.9)	0.17
Chronic lung disease	158 (12.7)	374 (14.8)	0.08
Chronic kidney disease	150 (12)	393 (15.6)	0.003
Chronic liver disease	58 (4.6)	161 (6.4)	0.02
Obesity	263 (21.2)	528 (42.5)	< 0.0001
Neurological disorder	100 (8.0)	162 (6.4)	0.06
Coronary heart disease	222 (17.9)	402 (16.0)	0.14
Heart failure	78 (6.2)	154 (6.1)	0.90
Immunosuppressant treatment	52 (4.1)	130 (5.1)	0.17
HIV	37 (2.9)	72 (2.8)	0.86
Pregnancy	32 (2.5)	81 (3.2)	0.23
Duration of symptom before testing, days	5.8 ± 3.5	8.2 ± 5.2	< 0.0001
Symptoms, no. (%)			
Fever	1,240 (100)	0 (0)	
Nasal congestion	210 (16.9)	121 (4.8)	< 0.0001
Sore throat	421 (33.9)	214 (8.5)	< 0.0001
Malaise	721 (53.1)	1,480 (58.9)	0.0008
Myalgia	892 (71.9)	1,829 (72.8)	0.57
Cough	324 (26.1)	723 (28.7)	0.08
Dyspnea	118 (9.5)	321 (12.7)	0.003
Anosmia	215 (17.3)	278 (16.4)	0.47
Ageusia	321 (25.8)	542 (24.4)	0.33
Rash	22 (1.7)	39 (1.5)	0.61
Headache	680 (54.8)	1,345 (53.5)	0.45
Diarrhea	86 (6.9)	132 (5.2)	0.03
Dizziness	343 (27.6)	362 (14.4)	< 0.0001
Others	182 (14.6)	542 (21.5)	< 0.0001
Severity of illness			
Non-hypoxic	933 (75.2)	1,854 (73.8)	0.35
Hypoxic	307 (24.8)	658 (26.2)	0.35
Mortality	35 (2.8)	82 (3.2)	0.50

SD: standard deviation.

risk factor for severe illness [5, 6]. However, hypertensive participants without DM had the lowest mortality. The prevalence of HT among non-survivors in studies analyzing risk factors for mortality due to COVID-19 state is as high as 46% and concludes that HT is a strong risk factor for severe illness and mortality [7]. It is likely that in prior studies, statistical co-linearity due to associated DM among those with HT influenced the outcome analysis. Given our observation, further analysis

Table 2. Comparison Between Symptoms and Outcomes Among Participants in Six Study Sub-Groups

Parameter	Diabetes mellitus ± additional illness (n = 1,364)		P	Hypertension ± additional non-diabetic chronic illness (n = 545)		P	Chronic lung disease (n = 428)		P	Chronic kidney disease ± HT (n = 339)		P	Chronic liver disease (n = 165)		P	Others (n = 911)		P
	FG (n = 443)	AFG (n = 921)		FG (n = 223)	AFG (n = 322)		FG (n = 118)	AFG (n = 310)		FG (n = 96)	AFG (n = 243)		FG (n = 42)	AFG (n = 123)		FG (n = 318)	AFG (n = 593)	
Fever	443 (100)	0		223 (100)	0(0)		118 (100)	0 (0)		96 (100)	0 (0)		42 (100)	0(0)		318 (100)	0 (0)	
Nasal congestion	96 (21.6)	32 (3.4)	< 0.001	9 (4.0)	12 (3.7)	0.85	13 (11.0)	8 (2.5)	0.0003	22 (22.9)	9 (3.7)	< 0.001	8 (19.0)	12 (9.7)	0.11	62 (19.4)	48 (8.0)	< 0.0001
Sore throat	182 (41.0)	62 (6.7)	< 0.001	42 (18.8)	21 (6.5)	< 0.001	32 (27.1)	18 (5.8)	< 0.001	18 (18.7)	8 (3.2)	< 0.001	12 (28.5)	12 (9.7)	0.003	135 (42.4)	93 (15.6)	< 0.0001
Malaise	391 (88.2)	621 (67.4)	< 0.001	102 (45.7)	204 (63.3)	< 0.001	60 (50.8)	260 (83.8)	< 0.001	30 (31.2)	42 (17.2)	0.004	20 (47.6)	18 (14.6)	< 0.0001	118 (37.1)	335 (56.4)	< 0.0001
Myalgia	416 (93.9)	718 (77.9)	< 0.001	118 (52.9)	206 (63.9)	0.009	72 (61.0)	120 (38.7)	< 0.001	32 (33.3)	118 (48.5)	0.01	24 (57.1)	123 (100)	< 0.0001	230 (72.3)	543 (91.5)	< 0.0001
Cough	112 (25.2)	224 (24.3)	0.70	51 (22.8)	112 (34.7)	0.002	26 (22.0)	176 (56.7)	< 0.001	12 (12.5)	114 (46.9)	< 0.001	8 (19.0)	54 (43.9)	0.004	115 (36.1)	43 (7.2)	< 0.0001
Dyspnea	24 (5.4)	64 (6.9)	0.28	11 (4.9)	40 (12.4)	0.003	24 (20.3)	92 (29.6)	0.052	12 (12.5)	70 (28.8)	0.001	16 (38.0)	51 (41.4)	0.701	31 (9.7)	4 (0.6)	< 0.0001
Anosmia	62 (13.9)	12 (1.3)	< 0.001	12 (5.3)	12 (3.7)	0.35	16 (13.5)	18 (5.8)	0.008	18 (18.7)	42 (17.2)	0.75	10 (23.8)	12 (9.7)	0.02	97 (30.5)	182 (30.6)	0.97
Ageusia	96 (21.6)	146 (15.8)	0.007	54 (24.2)	146 (45.3)	< 0.001	38(32.2)	41 (32.2)	0.99	36 (37.5)	68 (27.9)	0.08	31 (73.8)	48 (39.0)	0.0001	66 (20.7)	93 (15.6)	0.05
Rash	0	0		0 (0)	0 (0)	-	0 (0)	0 (0)		0 (0)	2 (0.8)		2 (4.7)	5 (4.0)	0.83	20 (6.2)	32 (5.3)	0.58
Headache	371 (83.7)	436 (47.3)	< 0.001	114 (51.1)	181 (56.2)	0.24	72 (61.0)	118 (38.0)	< 0.001	32 (33.3)	122 (50.2)	0.004	22 (52.3)	62 (50.4)	0.83	69 (21.6)	426 (71.8)	< 0.0001
Diarrhea	25 (5.6)	22 (2.3)	0.002	11 (4.9)	8 (2.4)	0.12	20 (16.9)	12 (3.8)	< 0.0001	3 (3.1)	34 (3.9)	0.70	4 (9.5)	14 (11.3)	0.74	23 (7.2)	42 (7.0)	0.93
Dizziness	114 (25,7)	62 (6.7)	< 0.001	72 (32.2)	38 (11.8)	< 0.001	32 (27.1)	112 (36.1)	0.07	14 (14.5)	42 (17.2)	0.54	22 (52.3)	32 (26.0)	0.001	89 (27.9)	76 (12.8)	< 0.0001
Others	60 (13.5)	182 (19.7)	0.004	18 (8.0)	46 (14.2)	0.026	20 (16.9)	56 (18.6)	0.68	16 (16.6)	62 (25.5)	0.07	9 (21.4)	22 (17.8)	0.60	59 (18.5)	174 (29.3)	0.0004
Non-hypoxic	341 (76.9)	741 (80.4)	0.13	196 (87.8)	284 (88.1)	0.91	72 (61)	222 (71.6	0.03	51 (53.1)	142 (58.4)	0.37	22 (52.4)	61 (49.5)	0.74	251 (78.9)	404 (68.1)	0.0006
Hypoxic	102 (23)	180 (19.5)	0.13	27 (12.2)	38 (11.8)	0.88	46 (38.9)	88 (28.3)	0.03	45 (46.9)	101 (41.6)	0.37	20 (47.6)	62 (50.4)	0.75	67 (21)	189 (31.8)	0.0005
Mortality	9 (2)	16 (1.7)	0.69	2 (0.8)	4 (1.2)	0.65	8 (6.7)	22 (7)	0.91	8 (8.3)	21 (8.6)	0.92	3 (7.1)	7 (5.6)	0.72	5 (1.5)	12 (2)	0.59

FG: febrile group; AFG: afebrile group; HT: hypertension.

of mortality among non-diabetic hypertensives is desirable. Our study observation on mortality among those with prior DM is comparable (2.6%, CI: 1.74 - 2.68) with reviews of published studies [8]. One of the largest studies (n = 4,716) on COVID-19 outcomes in patients with CKD with a higher proportion of participants with CKD stage 4 or higher observed a mortality of 44.6% which is much higher than our study which had a smaller proportion of advanced CKD patients [9]. Our study observed a relatively low mortality in patients with liver disease compared to prior studies (10-34%) which observed the outcome in a range of CLiDs (non-alcoholic fatty liver disease, chronic hepatitis-B infection, autoimmune hepatitis and cirrhosis) [10]. Similarly, the mortality among chronic obstructive pulmonary disease patients was lower compared to prior studies which report a case fatality rate of 4.3-61.5% [11]. While there are no large sample studies on effect of fever on the illness in a community cohort, a small sample study on 103 critically ill patients identified high fever (> 103 °F) despite optimal therapy as a risk for mortality [12]. Another study with a sample of 1,014, admitted to a temporary hospital in Wuhan, China prior to April 2020, identified high fever early in the course of illness as a risk factor for poor outcomes [13]. However, the study had limitation in the form of lack of clear definition for early fever and lack of separate analysis on fever characteristics in mild and severely ill patients [13].

We did not assess adjusted hazard ratio for the study, since the participants had variables which were difficult to adjust in analysis (degree of glycemic control, stage of CKD, stage of CLiD, baseline lung function, associated organ dysfunction, etc.) which showed a poor goodness of fit in models for hazard assessment. Study limitations include a lack of information on laboratory test results and details of treatment of study participants.

In conclusion, our study indicates that fever in COVID-19 is not associated with severe illness or mortality. The overall and risk factor specific mortality observed in our study is substantially low, probably due to lesser bias in selection of study participants or due to ethnicity of study population.

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Financial Disclosure

No financial assistance was obtained.

Conflict of Interest

All authors have no conflict of interest to declare.

Informed Consent

All participants provided written or digital informed consent.

Author Contributions

Concept and study design: EB, VS. Data collection and analysis: all authors. Write-up of manuscript: VS. Revision of manuscript: KV, EB.

Data Availability

The authors declare that data supporting the findings of the study are available within the article.

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