

## **Divergent: age, frailty, and atypical presentations of COVID-19 in hospitalized patients**

Paula Cristina Eiras Poco, MD<sup>1§</sup>; Márlon Juliano Romero Aliberti, MD, PhD<sup>1,2§\*</sup>; Murilo Bacchini Dias, MD<sup>1</sup>; Silvia de Fatima Takahashi, MD<sup>1</sup>; Fabio Campos Leonel, MD<sup>1</sup>; Marcelo Altona, MD<sup>1</sup>; Amanda Lagreca Venys Azevedo, MD<sup>1</sup>; Isabela Akie Shin-Ike, MD<sup>1</sup>; Bianca Aparecida Garcia, MD<sup>1</sup>; Leticia Harumi Sumita, MD<sup>1</sup>; Lara Mune de Oliveira Lima, MD<sup>1</sup>; Flavia Barreto Garcez, MD<sup>1</sup>; Thiago J. Avelino Silva, MD, PhD<sup>1</sup>

<sup>1</sup> Laboratorio de Investigacao Medica em Envelhecimento (LIM-66), Servico de Geriatria, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de Sao Paulo, Brazil.

<sup>2</sup> Research Institute, Hospital Sirio-Libanês, Sao Paulo, Brazil.

§: Both authors contributed equally to this work.

### **\* Address correspondence to:**

Márlon J. R. Aliberti

Laboratorio de Investigacao Medica em Envelhecimento (LIM-66)

Av. Dr. Eneas de Carvalho Aguiar 155, 8º andar, Clinica Medica, Sao Paulo, SP, Brazil

05403-000

E- mail: maliberti@usp.br

## Abstract

**Background:** Although frailty has been associated with atypical manifestations of infections, little is known about COVID-19 presentations in hospitalized frail patients. We aimed to investigate the association between age, frailty, and clinical characteristics of COVID-19 in hospitalized middle-aged and older adults.

**Methods:** Longitudinal observational study comprising 711 patients aged  $\geq 50$  years consecutively admitted to a university hospital dedicated to COVID-19 severe cases, between March and May 2020. We reviewed electronic medical records to collect data on demographics, comorbidities, COVID-19 signs/symptoms, and laboratory findings on admission. We defined frailty using the Clinical Frailty Scale (CFS=1-9; frail  $\geq 5$ ). We also documented in-hospital mortality. We used logistic regressions to explore associations between age, frailty, and COVID-19 signs/symptoms; and between typical symptoms (fever, cough, dyspnea) and mortality.

**Results:** Participants had a mean age of  $66 \pm 11$  years, and 43% were female. Overall, 25% were frail, and 37% died. The most common COVID-19 presentations were dyspnea (79%), cough (74%), and fever (62%), but patients aged  $\geq 65$  years were less likely to have a co-occurrence of typical symptoms, both in the absence (OR=0.56; 95%CI=0.39-0.79) and in the presence of frailty (OR=0.52; 95%CI=0.34-0.81). In contrast, older age and frailty were associated with unspecific presentations, including functional decline, acute mental change, and hypotension. After adjusting for age, sex, and frailty, reporting fever was associated with lower odds of mortality (OR=0.70; 95%CI=0.50-0.97).

**Conclusions:** Atypical COVID-19 presentations are common in frail and older hospitalized patients. Providers should be aware of unspecific disease manifestations during the management and follow-up of this population.

**Keywords:** COVID-19; signs and symptoms; laboratory tests; respiratory isolation; frailty.

## INTRODUCTION

Since the first reports of the Coronavirus Disease (COVID-19) in December 2019, there has been a rampant spread of the infection throughout the globe (1). In mid-July, more than 13 million cases have been confirmed, with almost 600 thousand deaths worldwide (2). The disease has a broad spectrum of clinical manifestations (1). While mild respiratory symptoms characterize most cases, approximately 19% of infected patients require hospitalization due to severe pneumonia and respiratory failure (3). Additionally, older adults have a higher risk of developing severe forms of the disease and account for half of the hospitalizations, and most deaths from COVID-19 (2).

Although fever, cough, and dyspnea are the most common symptoms of the new coronavirus disease, other less common features have been described (4). Gastrointestinal complaints, acute mental change, and functional decline are just some of the characteristics that have been observed in COVID-19 patients without fever or respiratory symptoms (5, 6). The possible lack of specific signs and symptoms of the disease raises concerns about the risk of misdiagnosis and the spread of the disease (5). For example, some case reports have addressed how the delay in isolating and treating individuals with atypical COVID-19 manifestations contributed to the nosocomial transmission of the SARS-CoV-2 virus (6).

Frailty has also been associated with atypical clinical presentations of infectious diseases. This syndrome is characterized by constriction of physiologic reserves and, consequently, by an impaired capacity to respond to acute insults (7). Moreover, frail patients are more likely to have chronic diseases and health deficits (e.g., cognitive, sensory, functional) that can mask the acute manifestations of infections and lead to a limited ability to recognize new symptoms (8, 9). Previous studies verified that up to 35% of frail older adults

with pneumonia did not report coughing, and up to 34% of those with bacteremia did not show signs of fever (8-10).

However, little is known about the clinical manifestations of COVID-19 in the context of frailty. A thorough understanding of the disease becomes particularly important in a scenario of overloaded health care settings, where prompt diagnoses are essential both to allocate resources and implement preventive measures (5). Therefore, we aimed to examine the manifestations of COVID-19 in hospitalized middle-aged and older adults and explore the association between age, frailty, and clinical characteristics of the infection.

## **METHODS**

### ***Study design and population***

Our work is part of the CO-FRAIL Project, an ongoing cohort study designed to investigate the association between frailty and adverse outcomes in patients aged 50 years and over hospitalized for COVID-19. The study takes in a tertiary university hospital located in Sao Paulo, the epicenter of the pandemic in Brazil. On March 30, 2020, one of the hospital's main buildings was converted to a COVID-19-only facility, dedicating 900 beds to the care of infected patients. Admissions to the COVID-19 care center are centrally managed by the Regulatory Central of the State of Sao Paulo, and referrals of severely ill patients are prioritized.

We assessed the eligibility of individuals aged 50 years and over who were consecutively admitted to the hospital between March 30 and May 20, 2020. We followed the World Health Organization's definitions of COVID-19 and included patients with probable (signs and symptoms of the disease + compatible findings in computed chest tomography, as

described by a radiologist + absence of a more likely alternative diagnosis) or confirmed (viral detection using reverse transcription-polymerase chain reactions) SARS-CoV-2 infection (11). We identified 750 eligible patients and excluded 39 cases with missing data on frailty criteria, resulting in a final sample of 711 participants.

Our local institutional review board approved the study and authorized that we obtain verbal consent to include participants in our cohort. We managed our database using Research Data Capture (REDCap) resources. Our cohort is listed in the Brazilian Clinical Trials Registry under the number RBR-7w5zhr.

Our local institutional review board approved the study protocol and authorized that we obtain verbal consent to include participants in our cohort.

### ***Data collection***

Trained medical investigators collected the study information using standardized electronic case report forms. Data were extracted from electronic medical records, nursing records, consulting notes, laboratory tests, and radiologic exams from the enterprise electronic health record reporting database (SOUL System; MV Hospitalar®). We were also able to review standardized forms that providers were required to complete for COVID-19 admissions. These forms detailed information of particular interest for COVID-19 patient care, including date of onset, signs, and symptoms of disease.

We documented length of hospital stay in days and the occurrence of in-hospital death.

## ***Measurements***

We retrieved information on demographics (age, sex, self-reported race or ethnicity, years of formal education, and marital status), comorbidities and burden of disease (Charlson Comorbidity Index), smoking status, number of medications in use, body mass index, vital signs and level of consciousness on admission [temperature, respiratory and heart rate, arterial blood pressure, oximetry, Richmond Agitation Sedation Scale (RASS)(12)], need for oxygen therapy (nasal cannula, face mask, or mechanical ventilation), and laboratory tests [complete blood count, D-dimer, C-reactive protein, urea, creatinine, electrolytes, bilirubin, transaminases, albumin, troponin, prothrombin time, and arterial blood gas analysis].

We reviewed medical histories checking for symptoms possibly related to COVID-19, including fever, cough (with or without sputum), dyspnea, myalgia, fatigue, sore throat, nasal congestion, runny nose, abdominal pain, diarrhea, anosmia, ageusia, headache, and skin rash. We also examined evidence of acute confusion as a surrogate measure of delirium using the CHART-DEL instrument (13), and functional decline (increased need for assistance in self-care activities in the 24 hours preceding admission). We defined fever, cough, and dyspnea as the most typical features of COVID-19 since they are the most commonly found complaints (3, 4).

For analysis purposes, we grouped participants as middle-aged (50-64 years old) or older adults ( $\geq 65$  years old). We classified the level of consciousness into three RASS categories: normal (0), hyperalert (+1 to +4), or hypoalert (-1 to -5), considering both hyperalert and hypoalert as altered level of consciousness (12). We used the neutrophil-to-lymphocyte ratio (NLR) as a measure of overall inflammatory status (14), and estimated glomerular filtration rates based on creatinine and patient characteristics. We also computed

the partial pressure of arterial oxygen to the percentage of inspired oxygen ratio ( $\text{PaO}_2/\text{FiO}_2$ ) to classify the patient's level of hypoxemia on admission (15). Reference ranges for each laboratory test are shown in **eTable 1 in the Supplement**.

### *Frailty assessment*

We measured frailty using the Clinical Frailty Scale (CFS), a nine-level global frailty rating scale based on clinical judgment (scores range from 1=very fit to 9=terminally ill) (7). CFS has been widely used in clinical practice and research on hospitalized older adults (16). The instrument assesses: (a) physical activity level; (b) symptoms that limit activities (e.g., being "slowed up" or tired); (c) dependence in basic and instrumental activities of daily living (ADLs and IADLs); (d) cognition. We followed previous work to define the presence of frailty as scores  $\geq 5$  (16).

In our study, investigators trained in geriatric medicine scored the CFS combining information from medical records with assessments completed by structured telephone interviews with patients or their proxies just after their inclusion in the study (17). We defined baseline health status as 15 days preceding the onset of acute infection symptoms and used baseline conditions to characterize frailty. Collected information included reported physical activity levels, number of falls in the last year, visual and hearing deficits, history of cognitive impairment, fatigue, weight loss in the last year, and functional status according to the Older Americans' Resources and Services Multidimensional Functional Assessment Questionnaire ADL section (18).

## *Statistical analysis*

We categorized our population according to four groups: (1) middle-aged participants without frailty; (2) middle-aged participants with frailty; (3) older participants without frailty; and (4) older participants with frailty. We then investigated differences across groups using the chi-square test for categorical variables and the one-way-analysis of variance or the Kruskal-Wallis test for interval variables. We also explored the association between older age, frailty, and the clinical features of COVID-19 using binary, ordinal, or multinomial logistic regressions that included each sign and symptom as the dependent variable and our age-frailty classification as the only independent variable.

Finally, we used logistic regression models to investigate the association between the occurrence of COVID-19 typical symptoms and in-hospital death in models unadjusted and adjusted for age, sex, and frailty. Statistical tests were two-tailed, and an alpha level  $<0.05$  determined significance. Analyses were conducted using Stata software, version 15.1 (Stata Corp., College Station, TX).

## **RESULTS**

In our total sample of 711 participants, the mean age was 66 years, and 43% were female. Overall, 64% were white, and 43% were married, with a median of five years of formal education (**eTable 2 in the Supplement**). We found frailty in 25% of our sample, with a higher prevalence in older adults when compared to middle-aged adults (35% vs. 15%;  $P <0.001$ ). We also observed that frailty was associated with being female and having sensory deficits and comorbidities (**eTable 3 in the Supplement**).



The frequency of several symptoms varied considerably according to age group and frailty diagnosis (**Table 1**). Notably, the co-occurrence of the typical features of COVID-19 (fever, cough, and dyspnea) was lower in frail and older participants; fever was reported much less frequently in frail patients, regardless of age. In contrast, frail participants were more likely to present unspecific manifestations of disease, such as acute confusion and acute functional decline (**Table 1**). **Figure 1** illustrates the association between COVID-19 clinical features and frailty, according to age group, and highlights how frailty and older age were associated with the absence of typical symptoms.

We verified that older adults, regardless of frailty, had a higher prevalence of hypotension, low body temperature ( $<36^{\circ}\text{C}$ ), and altered level of consciousness on admission (**Table 1; Figure 2**). Older adults also had significantly higher neutrophil counts, neutrophil-to-lymphocyte ratios, and urea, and lower glomerular filtration and albumin levels (**eTable 4 in the Supplement**). Moreover, frail patients from both age groups had lower levels of hemoglobin and lymphocytes, and higher levels of D-dimer and troponin on admission (**eTable 4 in the Supplement**).

The median length of hospital stay was 11 days, and we did not observe significant differences across age and frailty groups ( $P=0.60$ ). Our general mortality reached 37% and was particularly high among frail patients, in both middle-aged (frail=43% vs. non-frail=24%;  $P=0.004$ ) and older adults (frail=58% vs. non-frail=42%;  $P=0.003$ ). The co-occurrence of COVID-19 typical symptoms (fever, cough, and dyspnea) was associated with lower mortality in the unadjusted model (odds ratio [OR]= 0.72; 95% confidence interval [CI]= 0.52-0.98), but this finding did not remain after adjusting for age, sex, and frailty (OR=0.81; 95%CI=0.58-1.13). However, reporting fever was associated with lower odds of

mortality even after adjustment for the same set of confounders (OR=0.70; 95%CI=0.50-0.97).

## DISCUSSION

In this study, we completed a large sample of adults admitted to the hospital for COVID-19 and found that older age and frailty were associated with unspecific signs and symptoms of the disease. We found that the co-occurrence of the typical symptoms of the disease, including fever, cough, and dyspnea, was absent in the majority of frail and older patients. In contrast, these patients were more likely to experience atypical manifestations of COVID-19, such as functional decline, hypotension, and key features of delirium, including acute confusion and altered level of consciousness. Interestingly, reporting fever was associated with lower odds of mortality.

Atypical presentations of infectious diseases in frail and older adults can result from several factors. Frailty may pronounce the alterations of immunosenescence affecting the innate and adaptive immune systems in older adults (19). In frail older patients, changes in innate immunity were already linked to blunted or absent fever, and changes in adaptive immunity had been associated with lymphopenia, corroborating our findings. As we observed in our sample, older age and frailty are also associated with a higher prevalence of comorbidities, including dementia, and visual and hearing deficits, which can impair the ability to recognize and report symptoms of the acute disease (9). Chronic medical complaints (e.g., tachypnea in patients with heart failure) and medications in use (e.g., beta-blockers modifying chronotropic responses) are some of the other variables that may confound the expected manifestations of infectious diseases (8).

One additional concern is that unspecific features of COVID-19 could indicate higher severity of the infection (9). In our sample, older patients were more likely to be septic on admission, often presenting with hypotension and acute changes in mental status—acute confusion and altered level of consciousness that are common manifestations of delirium. Previous work with this cohort showed that delirium was strongly associated with admission to intensive care, ventilator utilization, and in-hospital death (13). Likewise, frail older adults had higher levels of neutrophil-to-lymphocyte ratio, lactate, D-dimer, and troponin, and lower platelet counts than middle-aged patients without frailty. All these biomarkers are indicative of systemic dysfunction and poor prognosis in SARS-Cov-2 infected patients (20). Our findings suggest that the new coronavirus might lead to more severe systemic injuries in this subgroup of patients, an assumption supported by the high mortality of frail and older individuals in our sample.

Our results have implications for patient care and education. Despite the widespread scenario of limited healthcare resources, providers should be careful to discard the hypothesis of COVID-19 in acutely ill frail older patients, even in the absence of symptoms like fever (5). Given the importance of social distancing and respiratory isolation to control the pandemic, patients and caregivers also need to be educated on the possibility that atypical presentations such as functional decline and acute mental change (i.e., delirium) might result from the new coronavirus. This knowledge can directly impact prompt testing and isolation measures (5, 6).

This study has important strengths. While most existing studies on the topic are case reports or series, we investigated presentations of COVID-19 in a large sample of hospitalized adults, which enabled us to explore the association between age, frailty, and features of the disease. We were also able to obtain detailed clinical information on our

patients, using data not only from medical records but from structured telephone interviews as well. Our study also had limitations. Its retrospective design prevented us from analyzing the timeline of COVID-19 manifestations, which would have helped us understand whether older patients present systemic symptoms before severe respiratory distress. Additionally, we completed our work in a single research center dedicated to high-complexity medical care, which might have biased the occurrence of some COVID-19 symptoms, such as dyspnea. Even so, we were able to find significant differences in clinical presentations according to age group and frailty status, and these associations should hold in the context of COVID-19 hospital care.

In conclusion, frail older adults often did not experience the most typical features of COVID-19. Providers should be aware of unspecific manifestations of diseases during the management and follow-up of this population. Future research should also examine the presentations of COVID-19 in other geriatric settings, such as in long-term care facilities.

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### ***Conflicts of Interest***

The authors declare no conflicts of interest.

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### ***Author Contributions:***

P.C.E.P., M. J. R A., M.B.D., T.J.A.S.: study concept and design, data analysis, data interpretation, and manuscript preparation.

S.F.T., F.C.L., M.A., A.L.V.A., F.B.G.: acquisition of data, study concept and design, data interpretation, and manuscript preparation.

I.A.S., B.A.G., L.H.S., L.M.O.L: acquisition of data, data interpretation, and manuscript preparation.

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## CAPTIONS FOR TABLES AND ILLUSTRATIONS

**Table 1.** Signs and symptoms on the admission of hospitalized COVID-19 patients according to age group and frailty diagnosis.

**Figure 1. Association between age, frailty, and COVID-19 symptoms in hospitalized patients (n=711).**

Point estimates (and their 95% confidence intervals) were calculated using unadjusted logistic regressions, including each symptom in the models as the dependent variable and the classification according to age and frailty as the independent variable; non-frail and middle-aged participants composed the reference group.

Typical symptoms were defined as the co-occurrence of fever, cough, and dyspnea. Upper respiratory tract symptoms combined nasal congestion, runny nose, or sore throat.

**Figure 2. Association between age, frailty, and COVID-19 signs in hospitalized patients (n=711).**

Point estimates (and their 95% confidence intervals) were calculated using unadjusted logistic regressions, including each sign in the models as the dependent variable and the classification according to age and frailty as the independent variable; non-frail and middle-aged participants composed the reference group.

Hypoxemia was defined as mild (200 to 300 mmHg), moderate (100 to 200 mmHg), or severe ( $\leq 100$  mmHg) according to the ratio of arterial oxygen partial pressure to fractional inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ).

**Table 1.** Signs and symptoms on the admission of hospitalized COVID-19 patients according to age group and frailty diagnosis.

Variables	Middle-aged adults		Older adults		P-value <sup>a</sup>
	Non-frail (n = 290)	Frail (n = 51)	Non-frail (n = 240)	Frail (n = 130)	
<b>Symptoms, n (%)</b>					
Fever	210 (72.4)	27 (52.9)	134 (55.8)	67 (51.5)	<0.001
Cough	228 (78.6)	38 (74.5)	176 (73.3)	83 (63.8)	0.017
Dyspnea	226 (77.9)	42 (82.4)	190 (79.2)	106 (81.5)	0.80
Co-occurrence of typical symptoms <sup>b</sup>	136 (46.9)	19 (37.2)	79 (32.9)	41 (31.5)	0.002
Myalgia	100 (34.5)	7 (13.7)	62 (25.8)	19 (14.6)	<0.001
Fatigue	86 (29.7)	10 (19.6)	92 (38.3)	39 (30.0)	0.029
Upper respiratory tract symptoms <sup>c</sup>	48 (16.6)	2 (3.9)	32 (13.3)	15 (11.5)	0.083
Diarrhea or abdominal pain	53 (18.3)	6 (11.8)	34 (14.2)	13 (10.0)	0.13
Anosmia or ageusia	48 (16.6)	4 (7.8)	34 (14.2)	3 (2.3)	<0.001
Headache	59 (20.3)	4 (7.8)	36 (15.0)	3 (2.3)	<0.001
Acute confusion	16 (5.5)	12 (23.5)	25 (10.4)	45 (34.6)	<0.001
Acute change from baseline function	133 (46.2)	27 (54.0)	138 (58.2)	86 (67.7)	<0.001
Number of symptoms (0-11), median (IQR)	4 (3-5)	3 (3-4)	4 (3-5)	4 (3-5)	0.003
Days of symptoms, median (IQR)	8 (6-12)	5 (2-10)	7.5 (5-11)	7 (4-9)	<0.001
<b>Signs, n (%)</b>					
Body temperature (°C)					<0.001
< 36°C	40 (13.8)	11 (21.6)	60 (25.0)	33 (25.4)	
36°C–37.2°C	190 (65.5)	32 (62.7)	152 (63.3)	90 (69.2)	
≥ 37.3°C	60 (20.7)	8 (15.7)	28 (11.7)	7 (5.4)	
Respiratory rate					0.004
≤ 20 breaths/min	81 (27.9)	24 (47.1)	78 (32.5)	56 (43.1)	
21–29 breaths/min	140 (48.3)	22 (43.1)	119 (49.6)	58 (44.6)	
≥ 30 breaths/min	69 (23.8)	5 (9.8)	43 (17.9)	16 (12.3)	
Oxygen therapy at triage					<0.001
None (ambient air)	94 (32.4)	19 (37.3)	62 (25.8)	25 (19.2)	
Nasal cannulas or face masks	142 (49.0)	26 (51.0)	106 (44.2)	78 (60.0)	
Mechanical ventilation	54 (18.6)	6 (11.8)	72 (30.0)	27 (20.8)	
Moderate/severe hypoxemia <sup>d</sup>	113 (39.0)	10 (19.6)	108 (45.0)	46 (35.4)	0.006
Tachycardia (> 100 beats/min)	74 (25.5)	16 (31.4)	47 (19.6)	17 (13.1)	0.009
Hypotension (BP < 90/60 mmHg)	34 (11.7)	10 (19.6)	65 (27.1)	31 (23.8)	<0.001
Level of consciousness					<0.001
Normal	228 (78.6)	40 (78.4)	159 (66.3)	80 (61.5)	
Hyperalert	21 (7.2)	6 (11.8)	22 (9.2)	28 (21.5)	
Hypoalert	41 (14.1)	5 (9.8)	59 (24.6)	22 (16.9)	

Note: IQR = interquartile range; BP = blood pressure.

<sup>a</sup> Comparisons were performed across age-frailty groups. For categorical variables, we used the chi-square test; and for continuous variables, we used the Kruskal- Wallis test.

<sup>b</sup> Defined as the co-occurrence of fever, cough, and dyspnea, the most common COVID-19 symptoms.

<sup>c</sup> Nasal congestion, runny nose, or sore throat.

<sup>d</sup> Defined for a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) ≤200 mmHg.

Figure 1

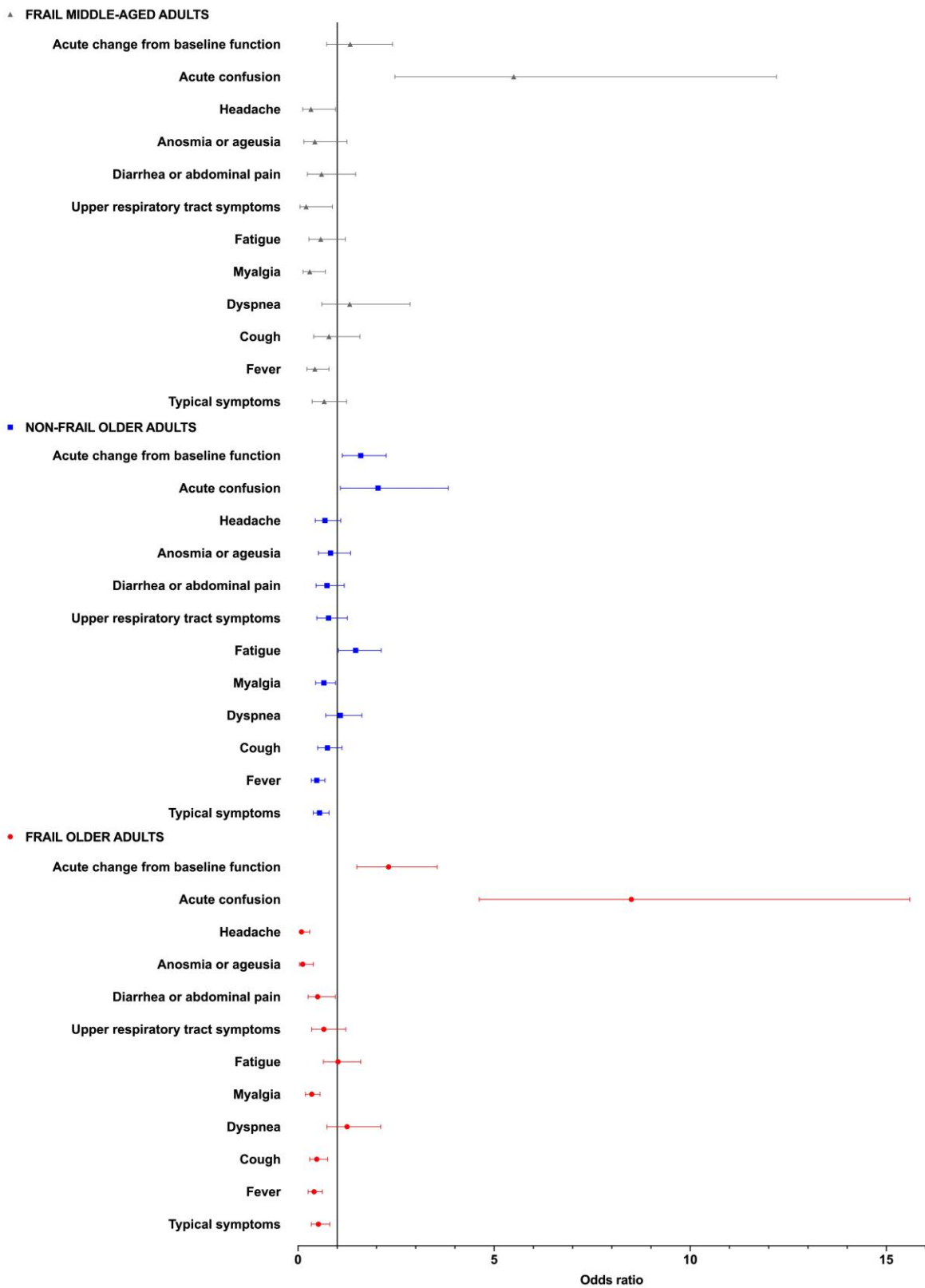
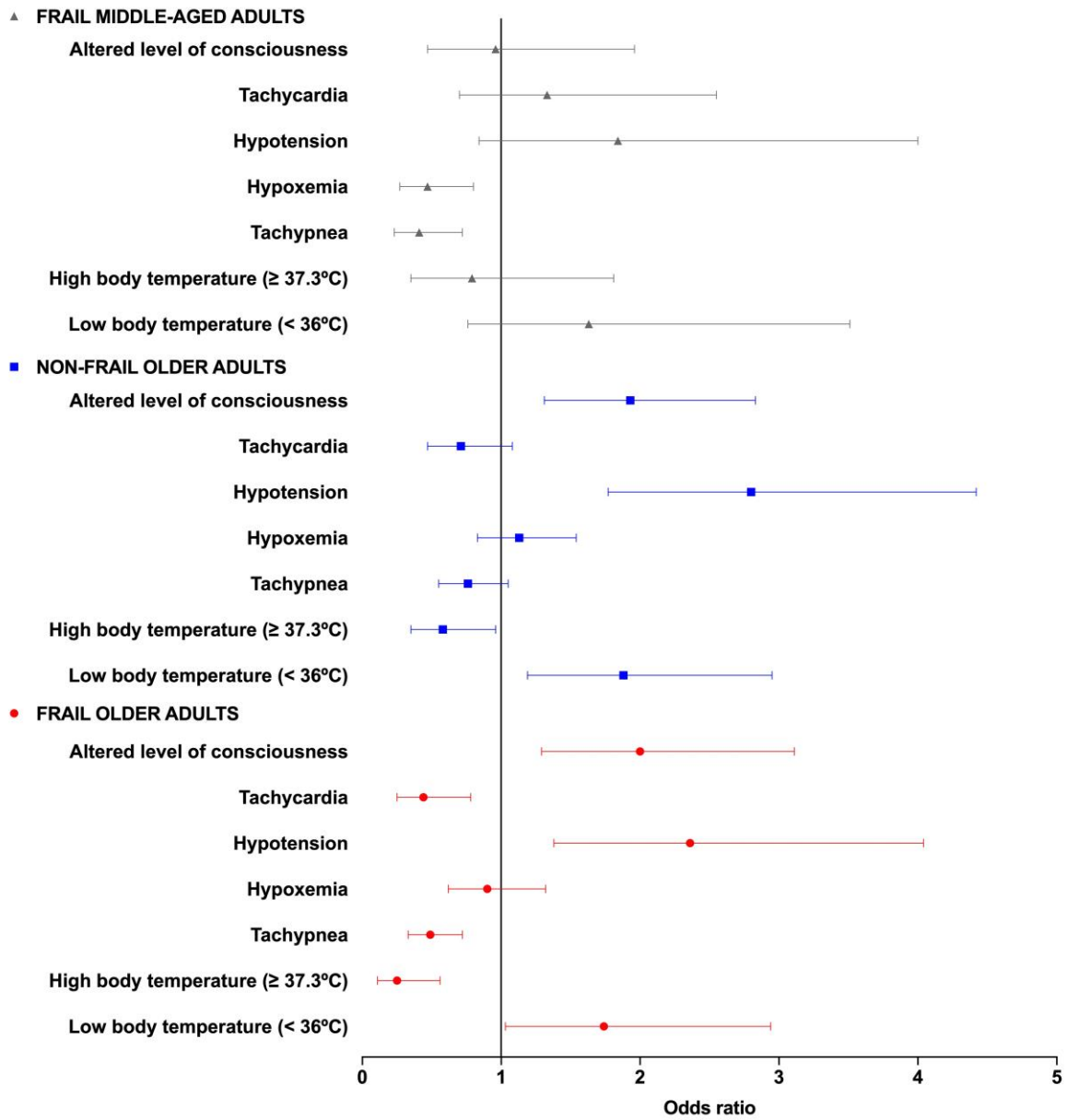


Figure 2



ACC