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# Predictors of disease duration and symptom course of outpatients with acute COVID-19: a retrospective cohort study



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**Title:** Predictors of disease duration and symptom course of outpatients with acute covid-19: a retrospective cohort study

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## ABSTRACT

**Objective:** Describe the disease course in a cohort of outpatients with covid-19 and evaluate factors predicting duration of symptoms

**Design:** Retrospective cohort study

**Setting:** Telemedicine clinic at a large medical system in Atlanta, Georgia

**Participants:** 273 patients with COVID-19. Exclusion criteria included: (1) intake more than 10 days after symptom onset, (2) hospitalization for covid-19, (3) symptoms at less than two visits.

**Main outcome measures:** Symptom duration in days

**Results:** Common symptoms at diagnosis are upper respiratory (64% cough, 53% loss of smell or taste, 50% sinus congestion, 22% sore throat), systemic (50% headache, 48% body aches, 36% chills, 22% dizziness, 18% fever). The most frequent remaining symptoms at 30 days were cough (7%), loss of smell or taste (5%), body aches (5%), nasal congestion (5%), shortness of breath with exertion (5%), and joint pain (5%). Day of symptom onset was earliest for upper respiratory symptoms (mean 1.26 days, 95% confidence interval 1.15 to 1.4), followed by systemic symptoms (1.54, 1.39 to 1.7), with later onset of lower respiratory (2.86, 2.54 to 3.22) and gastrointestinal symptoms (3.46, 3.07 to 3.89), when present. Cough had the longest duration when present with 12.2 days (10.9 to 13.6). Loss of smell or taste had the second longest duration with 11.0 days (9.9 to 12.2). Provider-Assessed Symptom Severity (PASS) is the best predictor of symptom duration ($P < 0.005$ for multiple symptoms) and patients with "Moderate" PASS compared to "Mild" at their intake visit have higher rates of symptoms at 30 days, including cough (12%), nasal congestion (10%), joint pain (10%), body aches (9%), loss of taste or smell (7%), headache (7%), and shortness of breath with exertion (6%).

**Conclusions:** Covid-19 illness in outpatients follows a pattern of progression from systemic symptoms to lower respiratory symptoms and persistent symptoms are common across categories. Provider-assessed symptom severity is the best predictor of disease duration.

**Strengths and limitations of this study**

Strengths:

- By systematically calling patients throughout acute illness, we are able to provide a clear visual representation of symptoms of acute illness in outpatients.
- There is minimal missing data due to the nature of our clinic (following enrolled patients until resolution).
- We used standardized visits and templates for all patients and therefore are able to analyze predictors of symptom duration for specific variables including age, comorbidities and symptom severity.

Limitations

- We are a single center study with limited patient numbers (and low numbers of some comorbidities).
- We do not follow patients for long-term symptoms and therefore cannot define a specific end date for all symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Covid-19 symptoms in non-hospitalized adults span multiple organ systems, most often including respiratory and systemic symptoms

Symptom duration varies substantially between patients, ranging from brief (days) to prolonged (weeks to months)

WHAT THIS STUDY ADDS

Disease duration is predicted by early symptom severity during the acute illness

Disease course can be described in a pattern with early systemic symptoms, followed by lower respiratory and, less often, gastrointestinal symptoms

Multiple symptoms may persist to 30 days, most often cough, loss of smell or taste, sinus congestion, shortness of breath on exertion, body aches, and headache

## INTRODUCTION

Coronavirus disease 2019 (covid-19) has brought large numbers of patients to medical attention within a span of months for care of a previously undescribed illness. Early reports on the presentation and natural history of covid-19 appropriately focused attention on the severe cases and critically ill.[1-5] Subsequent surveillance has demonstrated that the majority of patients have milder forms of illness [6] and it is recommended that they remain at home with medical supervision.[7,8] Although the duration of home isolation is defined based on symptoms,[7] understanding of the symptom course of outpatients with covid-19 is limited and most reports include presenting symptoms alone or cross-sectional follow-up information.[9-17] Longitudinal symptom data and predictors of individual symptom duration have not been described.

In March 2020, we established a virtual clinic for the care of patients in home isolation with covid-19: the "Virtual Outpatient Management Clinic" (VOMC), using available knowledge for assessment and treatment guidelines. All patients underwent telemedicine intake visits with a physician or advanced practice provider (APP), including assessment of specific covid-19 symptoms using a standardized clinical note. Patients were followed for symptom management with regular telephone calls by registered nurses (RNs) and APPs until improvement or hospitalization.

As it became clear in clinical practice that symptom duration varies substantially between patients, we undertook this study to determine the predictors of symptom course of our VOMC

cohort. We hypothesized that risk factors for covid-19 complications severity (demographics, comorbidities, symptom severity) would predict symptom duration.

## METHODS

### Study setting

The study was a retrospective cohort study, conducted at Emory Healthcare, the largest academic health system in Georgia (serving the greater Atlanta metropolitan area), which includes more than 250 provider locations and 120 primary care locations. The VOMC comprised an intake team of 14 physicians and 3 APPs from two primary care clinics; and follow-up call teams included 19 redeployed registered nurses (RNs) and 20 APPs. All intake providers were trained in the use of the risk assessment tool in a one-hour webinar and conducted a median of 25 intake visits during the study period (range: 5-99), with the majority of intake visits conducted by physicians (83.6%).

### Study cohort

We included outpatient adults who completed their VOMC intake visit between 24 March 2020 and 26 May 2020 with initial symptom dates between 17 March and 20 May. Exclusion criteria were: (1) intake visit more than 10 days after symptom onset, (2) hospitalization for covid-19 at any time, (3) symptoms at less than two visits (i.e. to be included, we required a minimum of one symptom reported during at least 2 separate visits, including intake visit and follow-up calls). We chose the exclusion criteria a priori in order to improve the accuracy of early symptom reporting and completeness of follow-up.

Subsets from this cohort have been reported elsewhere in a small case series[18] and for hospitalization risk prediction,[19] but the current study is the first to analyze complete longitudinal symptom reporting for the cohort.

During the study period, outpatient covid-19 testing was conducted by medical providers using nasopharyngeal sampling for real-time reverse transcription–polymerase chain reaction (RT-PCR) detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Adult patients with positive RT-PCR results from the screening clinics or emergency departments were called by a result notification team to provide self-care advice and refer for enrollment in the VOMC. The details of care are outlined in Box 1. Overall symptom severity was assessed by the Provider-Assessed Symptom Severity (PASS) criteria in Box 1. It was based primarily on respiratory symptoms.

BOX 1: Virtual Outpatient Management Clinic Care

**Outpatient covid-19 testing criteria (March-April 2020):**

1. Either (a) fever, cough, or shortness of breath or (b) two symptoms from the following: sore throat, congestion, myalgias, fatigue, diarrhea, loss of smell.
2. Prioritize: (a) frontline healthcare workers, (b) students on-campus and health professions, (c) CDC employees, (d) patients with risk factors (age, comorbidity, immunosuppression, work in a communal setting).

**VOMC enrollment criteria:**

1. Diagnosis of covid-19 by nasopharyngeal PCR, and
2. Requiring outpatient management of covid-19 symptoms

**Intake telemedicine visit:**

1. Documentation template includes symptom history, symptom severity (patient-reported and provider-assessed), past medical history, physical examination and risk assessment.
2. Symptoms assessed: "systemic" (fever, chills, body aches, dizziness, confusion, headache, joint pain), "upper respiratory" (loss of smell or taste, sinus congestion, sore throat, cough), "lower respiratory" (chest tightness, shortness of breath with exertion, shortness of breath at rest, wheezing), "gastrointestinal" (abdominal pain, nausea, diarrhea), and rash. Note: symptoms assessed as a single list and not grouped into categories during assessment.
3. Provider gives advice for (1) symptom management, (2) home isolation guidance and (3) outpatient monitoring.

**Provider-Assessed Symptom Severity definition:**

1. Mild
    a. Respiratory: Cough, sputum production
    b. Systemic: Fever, chills, malaise, myalgia, anorexia, diarrhea, vomiting, headache
2. Moderate
    a. Respiratory: Severe cough, dyspnea on exertion, wheezing or sensation of mid-chest tightness
    b. Systemic: N/A (Not provided in VOMC clinical guideline)
3. Severe
    a. Resting dyspnea, labored breathing, resting pulse oximetry ≤92%, pleuritic pain, hemoptysis
    b. Systemic: acute confusion, severe weakness, syncope, acute decline in functional status

**Follow-up phone calls (March-June 2020):**

1. Patients receive follow-up telephone calls on the following schedule:
    a. Low risk: every other day for a minimum of 7 days from symptom onset
    b. Intermediate risk: daily for a minimum of 14 days from symptom onset
    c. High risk: twice daily for a minimum of 21 days from symptom onset
2. All patients called until the intervals above and for a minimum 3 days after improvement in fevers (without antipyretics) and improvement in respiratory symptoms (whichever criteria was longer).
3. Patients with improving or worsening symptoms could change tier after enrollment at provider discretion.

## Data sources

Study data were obtained from two specific provider notes types deployed in March 2020 within the Emory Healthcare electronic health record (Cerner Corp., Kansas City, Missouri, United States): (1) VOMC provider intake assessment and (2) VOMC follow-up telephone call.

The intake assessment note template included (1) documentation of specific covid-19 symptoms including onset and offset dates, (2) patient reported and provider-assessed symptom severity (PASS), and (3) documentation of specific medical conditions associated with risk of severe covid-19 (based on medical literature search in March 2020). The follow-up telephone call template included an identical symptom list with "yes/no" selection for documentation of the presence or absence of symptoms at follow-up.

If symptom onset date was not identified in VOMC notes, we conducted manual chart review of telephone records prior to VOMC enrollment. Additional demographic information including age, gender, and race (if recorded) was included from the electronic health record.

To ensure that symptoms were counted only once a day per patient, among patients receiving 2 calls per day, if a symptom was listed as present more than once for a particular day, it was counted only once. Among patients receiving calls every other day, if a symptom was present on both the preceding and subsequent day it was listed as present on the single non-call day in between for symptom duration.

**Main outcomes**

The main outcome was symptom duration in days. The outcomes were the durations for each specific symptom. For symptoms not present on all dates (i.e. waxing and waning), we used the first and last documented dates of the symptom to document duration. The secondary outcome was the day of symptom onset. Symptoms were groups into systems: upper

respiratory (cough, congestion, sore throat, loss of smell or taste), systemic (body aches, chills, dizziness, headache, joint pain), lower respiratory (shortness of breath with exertion, shortness of breath at rest, chest tightness) and gastrointestinal (nausea, abdominal pain, diarrhea). Clinical record extraction was conducted 21 June 2020 at which time all enrolled patients had at least 30 days of follow up based on symptom start date and all patients had received their final VOMC nurse call.

**Bias**

Screening criteria are noted in Box 1. Healthcare employees were prioritized in the screening process and may be overrepresented in the cohort. Patient enrollment in VOMC was voluntary at the time of results notification, which may result in selection bias. Patients were scheduled for the minimum recommended follow-up calls at the time of intake (and could later extend care further if needed) but could disengage on request, which could lead to attrition bias.

**Predictors**

Demographics, comorbidities, patient reported symptom severity and PASS were tested as predictors of disease duration.

**Statistical analysis**

Duration of symptoms (in days) was found to have a positive skew so a natural logarithmic transformation was used. This was compared to a gamma loglink, negative binomial with loglink and a square root transformation of duration. The natural logarithmic transformation

was chosen because it had the smallest Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC). Mean durations and 95% confidence interval were calculated based on the log transformation and then exponentiated back to obtain the result in days. One-way ANOVA was used to compare the mean log durations for each symptom between different groups for each predictor. Because multiple comparisons are being made we were looking for p values < 0.005 rather than 0.05. Different predictors significant to this level were to then be included in a multi-way ANOVA. The results were then exponentiated back from natural log of days to days for results.

Similarly, the day of symptom onset organized by systems was found to be positively skewed. In this case a natural logarithmic transformation was also used because it had a smaller AIC and BIC than the gamma log link and negative binomial with loglink of start day. Square root transformation of start day had a slightly better AIC (2108 vs 2161) and BIC (2132 vs 2185) than the logarithmic transformation, but we used the logarithmic transformation to maintain consistency with symptom duration (which was transformed with a natural logarithm). ANOVA compared the day of symptom onset between the different systems (systemic, upper respiratory, lower respiratory and gastrointestinal). After analysis the natural exponent was taken of the results to present the result in day of symptom onset.

**Patient and public involvement**

Patients and the public were not involved in the design and conduct of the study, outcomes, recruitment, or planned dissemination.

**RESULTS:**

551 intake visits were completed in VOMC between 24 March 2020 and 26 May 2020. We included 273 patients in the study after excluding: 123 patients with intake visit more than 10 days after symptom onset, 62 patients hospitalized at any time for covid-19, 57 patients with symptoms on less than two visits, 26 patients that did not receive follow up calls, 7 patients without documented positive RT-PCR test for SARS-CoV-2, and 3 patients with blank or uninterpretable symptom entries.

**Characteristics of the study population**

Table 1 describes demographics, comorbidities, and symptoms at intake visit for the cohort. Since subsequent analysis showed only symptom severity as significantly predicting disease duration, we also describe our cohort by PASS. With all patients hospitalized for covid-19 excluded, we only had four patients with PASS "severe" in our study. All four were black women, and their only comorbidities were asthma, hypertension, and obesity. There was no statistically significant difference in age by PASS. Patients in our study had mean age 45.7 years, 69% women, and 47% black. The PASS groups differed significantly ($p<0.05$) for comorbidities asthma and immunosuppression.

**Table 1 Demographics, comorbidities and symptoms at initial visit**

| | Provider Assessed Symptom Severity (PASS) | | | | ANOVA mod vs severe p |
|---|---|---|---|---|---|
| | Total (n=273) | Mild (n=164) | Moderate (n=86) | Severe (n=4) | |
| Demographics: | | | | | |
| Age, mean (95% CI, ANOVA p value) | 45.7 (44.0-47.5) | 44.6 (42.4-46.8, ref) | 48.2 (45.0-51.4, 0.143) | 51 (43.8-58.2, 0.651) | 0.923 |
| Days, mean (95% CI, ANOVA p value) | | | | | |
| Symptom onset to first VOMC visit | 5.68 (5.37-5.99) | 5.58 (5.16-6.00, ref) | 5.91 (5.43-6.39, 0.338) | 6.00 (2.56-9.44, 0.746) | 0.943 |
| Symptom onset to last phone call | 20.9 (19.84-21.95) | 18.63 (17.46-19.8, ref) | 24.62 (22.73-26.50, <0.001) | 34.25 (21.63-46.87, < 0.001) | 0.002 |
| Count, (%) | | | | | $Chi^2$ p value |
| Gender, women | 189 (69.2%) | 122 (74.4%) | 63 (73.3%) | 4 (100%) | 0.481 |
| Gender, men | 84 (30.8%) | 56 (34.1%) | 28 (32.6%) | (0%) | |
| Race, black | 129 (47.3%) | 79 (48.2%) | 46 (53.5%) | 4 (100%) | 0.261 |
| Race, white | 44 (16.1%) | 28 (17.1%) | 16 (18.6%) | 0 (0%) | |
| Race, other/unknown | 81 (29.7%) | 57 (34.8%) | 24 (27.9%) | 0 (0%) | |
| Co-morbidities: | | | | | |
| Age>60 | 46 (16.8%) | 28 (17.1%) | 18 (20.9%) | 0 (0%) | 0.492 |
| Asthma | 35 (12.8%) | 14 (8.5%) | 20 (23.3%) | 1 (25%) | 0.011 |
| Coronary artery disease | 9 (3.3%) | 3 (1.8%) | 6 (7%) | 0 (0%) | 0.193 |
| Cancer | 20 (7.3%) | 15 (9.1%) | 5 (5.8%) | 0 (0%) | 0.615 |
| COPD | 2 (0.7%) | 0 (0%) | 2 (2.3%) | 0 (0%) | 0.145 |
| Diabetes | 32 (11.7%) | 19 (11.6%) | 13 (15.1%) | 0 (0%) | 0.541 |
| Drug abuse | 3 (1.1%) | 2 (1.2%) | 1 (1.2%) | 0 (0%) | 1.000 |
| Heart failure | 5 (1.8%) | 2 (1.2%) | 3 (3.5%) | 0 (0%) | 0.393 |
| Hypertension | 86 (31.5%) | 49 (29.9%) | 35 (40.7%) | 2 (50%) | 0.175 |
| Immunosuppression | 14 (5.1%) | 4 (2.4%) | 10 (11.6%) | 0 (0%) | 0.022 |
| Lung disease | 8 (2.9%) | 3 (1.8%) | 5 (5.8%) | 0 (0%) | 0.233 |
| Reported obesity | 77 (28.2%) | 47 (28.7%) | 29 (33.7%) | 1 (25%) | 0.781 |
| Renal disease | 7 (2.6%) | 4 (2.4%) | 3 (3.5%) | 0 (0%) | 0.727 |
| Symptom present at Initial Visit: | | | | | |
| Fever | 49 (17.9%) | 20 (12.2%) | 26 (30.2%) | 2 (50%) | <0.001 |
| Chills | 98 (35.9%) | 40 (24.4%) | 47 (54.7%) | 4 (100%) | <0.001 |
| Body aches | 130 (47.6%) | 62 (37.8%) | 60 (69.8%) | 3 (75%) | <0.001 |
| Dizziness | 60 (22%) | 20 (12.2%) | 34 (39.5%) | 2 (50%) | <0.001 |
| Confusion | 3 (1.1%) | 1 (0.6%) | 1 (1.2%) | 1 (25%) | 0.047 |
| Headache | 137 (50.2%) | 73 (44.5%) | 53 (61.6%) | 3 (75%) | 0.015 |
| Loss of smell or taste | 145 (53.1%) | 80 (48.8%) | 52 (60.5%) | 4 (100%) | 0.031 |
| Sinus congestion | 136 (49.8%) | 78 (47.6%) | 45 (52.3%) | 2 (50%) | 0.814 |
| Sore throat | 59 (21.6%) | 31 (18.9%) | 22 (25.6%) | 3 (75%) | 0.023 |
| Cough | 176 (64.5%) | 96 (58.5%) | 66 (76.7%) | 4 (100%) | 0.004 |

| | | | | | |
|---|---|---|---|---|---|
| Chest tightness | 77 (28.2%) | 29 (17.7%) | 37 (43%) | 4 (100%) | <0.001 |
| SOB at rest | 31 (11.4%) | 12 (7.3%) | 16 (18.6%) | 1 (25%) | 0.014 |
| SOB with exertion | 90 (33%) | 32 (19.5%) | 47 (54.7%) | 3 (75%) | <0.001 |
| Wheezing | 22 (8.1%) | 4 (2.4%) | 17 (19.8%) | (0%) | <0.001 |
| Abdominal pain | 32 (11.7%) | 14 (8.5%) | 16 (18.6%) | (0%) | .065 |
| Nausea | 48 (17.6%) | 20 (12.2%) | 25 (29.1%) | 1 (25%) | .003 |
| Diarrhea | 64 (23.4%) | 29 (17.7%) | 32 (37.2%) | (0%) | .002 |
| Join pain | 58 (21.2%) | 23 (14%) | 33 (38.4%) | 1 (25%) | <.001 |
| Rash | 9 (3.3%) | 5 (3%) | 3 (3.5%) | 1 (25%) | .193 |

COPD=Chronic Obstructive Pulmonary Disease, SOB=Shortness of Breath

**Symptoms at initial visit**

The symptoms reported by the cohort at the intake visit included 64% cough, 53% loss of smell or taste, 50% sinus congestion, 50% headache, 48% body aches, 36% chills, 33% shortness of breath with exertion, 28% chest tightness, 23% diarrhea, 22% dizziness, 22% sore throat, 22% joint pain, 18% fever, 11% shortness of breath, 8% wheezing, 3% rash (Table 1). The groups differed significantly except for rash, abdominal pain, and sinus congestion.

**Time course of individual symptoms**

Figure 1 displays the heat map of symptoms over a 30 day follow up period for all 273 patients by percentage of patients with symptoms. Among all patients, the most prevalent symptom reported during 30 days of follow up was cough (62%), loss of smell or taste (54%), body aches (52%), headache (50%), and nasal congestion (47%). The most frequent remaining symptoms at 30 days were cough (7%), loss of smell or taste (5%), body aches (5%), nasal congestion (5%), shortness of breath with exertion (5%), and joint pain (5%). Fever was not a prominent symptom during 30 days of follow up, present in 27% of patients early in the course of illness.

**Time course of symptoms by Provider-Assessed Symptom Severity**

The heat map findings for Mild PASS was similar to the entire cohort, with loss of smell or taste in 52% over 30 days and 4% at 30 days and cough in 54% over 30 days and 3% at 30 days of follow up (Figure 1). At 30 days, 3% of patients described both body aches and joint pain. The heat map for Moderate PASS had higher rates of cough (74%), body aches (71%), loss of taste or smell (60%), headache (57%), nasal congestion (55%), shortness of breath with exertion (53%), chills (53%), fever (36%), diarrhea (42%), joint pain (36%) and dizziness (35%). At 30 days the most prominent symptom remaining was cough (12%), nasal congestion (10%), joint pain (10%), body aches (9%), loss of taste or smell (7%), headache (7%), and shortness of breath with exertion (6%). The heat map for the four patients with Severe PASS shows 75% of patients experienced chills, body aches, headache, loss of smell or taste, sore throat, cough, chest tightness, and shortness of breath with exertion during 30 days of follow up. At 30 days, 3 patients (75%) still had cough.

**Timing of symptom onset of by system**

The day of symptom onset was earliest for upper respiratory symptoms, followed by systemic symptoms, with later onset of lower respiratory and gastrointestinal symptoms, when present (figure 2).

**Duration of each symptom**

Figure 3 describes the mean days and 95% confidence interval for each symptom followed in the cohort over 30 days. Cough had the longest duration with 12.2 days (95% confidence

interval 10.9 to 13.6, N=223). Loss of Smell or Taste had the second longest duration with 11.0 days (9.9 to 12.2, N=196).

**Symptom duration by Provider-Assessed Symptom Severity**

PASS and patient-reported symptom severity were the only two predictors of disease duration that met prespecified statistical significance with $p < 0.005$. PASS was significantly correlated with more symptoms on ANOVA and, thus, was chosen for the model. No other predictors, including demographics and comorbidities, met significance for more than a single symptom and therefore multi-way ANOVA was not performed. Figure 4 shows the duration of symptoms for the overall group alongside the duration for each PASS group. Body aches, shortness of breath with exertion, headache, diarrhea and congestion had significant difference in durations between mild and more severe PASS groups. Chest tightness had significant difference in duration in moderate versus severe PASS. Body aches, shortness of breath with exertion, dizziness and chest tightness did not reach the level of statistical significant we set out in methods likely due to the small number of patients in the severe PASS group. Loss of smell or taste also did not reach the threshold set out in methods section but we kept it to compare with other publications.

## DISCUSSION

### Principal findings

In this cohort of non-hospitalized patients with covid-19, disease course follows a pattern of progression that is illustrated with visual heatmaps of symptom frequency over time. The most common initial symptoms are systemic, upper respiratory and cough. Lower respiratory and gastrointestinal symptoms are less frequent and have a later onset in the disease course. The symptoms with the longest duration, when present, are cough, loss of smell or taste, sinus congestion, shortness of breath on exertion, body aches, and headache.

Patients were assigned a symptom severity (PASS) at the intake visit using a tool primarily aimed at determining hospitalization risk,[19] which was therefore based primarily on respiratory symptoms. Consistent with this, PASS is significantly associated with the presence of lower respiratory symptoms such as cough, chest tightness and shortness of breath with exertion. However, PASS was also associated with systemic symptoms (chills, body aches and dizziness) as well as greater incidence of symptoms from other organ systems (headache, loss of smell or taste, nausea, diarrhea). With clinical experience, it is possible that providers developed knowledge of other symptom categories and integrated these into the PASS. It is notable that sinus congestion, a common upper respiratory complaint, did not differ significantly between provider-rated severity groups.

An important observation in this study is that patient factors used to predict risk of severe disease (age, comorbidities) did not predict disease duration. Instead, we find that initial

provider assessment of symptom severity is the best predictor of disease duration. PASS predicts duration for a number of symptoms, with significant associations for respiratory symptoms as well as non-respiratory symptoms (including body aches, dizziness, chills, headache, and diarrhea). This highlights a role for clinical providers in the assessment of acute covid-19 and providing expectant counseling that may be difficult to replace with automated patient monitoring systems using self-reported symptom severity.

**Comparison with other studies**

Initial symptoms reported are similar to previous studies of mild covid-19 and non-hospitalized subsets.[12, 15] It differs from the overall reported literature, summarized in a recent systematic review of 148 studies.[14] Notably, fever was less common (n=49, 17.9%) compared with 78% in the systematic review, while other symptoms are more common, for example: headache (50.2% vs 13%), body aches (47.6% vs 17%), hyposmia (53.1% vs 25%). The higher frequency of multiple symptoms may be due to our systematic approach to symptom inquiry. Rate of fever may be underreported due to template wording “current fever” but also may be less frequent in this cohort as increased testing availability has expanded the symptom profile of “mild covid-19” patients eligible for screening.

We find that the course of illness and predictors of symptom duration have not been well described and this is an important contribution of this analysis. Narrative reviews have noted symptom progression similar to our report[21] and the visual course reported here in heatmap

form illustrates the development of respiratory symptoms during and after the first week of illness among patients never requiring hospitalization for covid-19.

The persistence of symptoms identified in our study is also an important finding for clinical practice. Patients and providers may be reassured that gradual resolution is typical based on our findings. In our experience providing in-person care, many patients present for evaluation of non-resolving symptoms during subacute or convalescent illness.[22] Other reports have noted long duration of medical leave among persons with covid-19, for example first responders in New York (leave duration mean 25.3 days, SD=13.2).[23] We are able to differentiate the likelihood of prolonged symptoms in patients using mild and moderate PASS, which may aid in clinical counseling and anticipation of symptom recovery times. Given reports of delayed recovery of symptoms after hospitalization,[24] the differentiation by symptom severity in outpatients is plausible.

**Strengths and limitations of study**

Our data on symptom course in outpatients is robust due to the structure of the VOMC, which was staffed to meet the anticipated "surge" of patients in March-May 2020 and therefore had skilled providers contacting patients and completing full note templates regularly through the course of acute illness. Missing clinical data were minimal (e.g. low risk patients contacted every 48 hours instead of 24 hours), allowing for standard approach to imputation.

The primary limitation of this study is that it represents a single-center cohort of patients screened during the early SARS-CoV-2 pandemic. Screening criteria favored the inclusion of working-age individuals in the cohort and our exclusion of hospitalized patients favors younger and healthier patients. We have limited numbers of patients with comorbidities and cannot therefore draw conclusions about the duration of symptoms related to specific conditions (e.g. chronic obstructive pulmonary disease).

Another limitation of the structured VOMC cohort data is the time to intake visit. Usual care requires a positive SARS-CoV-2 test prior to enrollment, and delays in testing could attenuate recall of initial symptoms. We therefore limited the study to patients within 10 days of symptom onset and used chart review to verify symptoms reported in the screening process. Discharge timing in the VOMC was a limitation for our follow-up data: the VOMC discharge criteria mirrored the CDC terminology of symptom "improvement," but not resolution. We find in other work (unpublished data) that minor residual symptoms are common after VOMC discharge (reported in 55 of 158, 34.8%, of patients contacted a mean of 37.9 days after discharge) and that few (n=7, 4.4%) have symptoms requiring medical follow-up (e.g. by a primary care physician or specialist).[25] These residual symptoms are not captured in the heatmap data after their final VOMC call.

**CONCLUSION**

Overall, we find that the symptom course of outpatients with covid-19 follows a pattern described in early observations with a typical illness course progressing from early symptoms (systemic, upper respiratory, and cough) to lower respiratory and gastrointestinal symptoms. We confirm that symptoms of altered smell or taste and headache are common in outpatients. Prolonged symptoms are common and the severity of symptoms in the acute phase of illness is the most significant predictor of disease duration.

## MANUSCRIPT INFORMATION

### Ethics

The study was approved by the Emory University Institutional Review Board (STUDY00000766), which granted both a waiver of informed consent and a waiver of the Health Information Portability and Privacy Act as the study posed no more than minimal risk.

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**Data Sharing Statement**: Deidentified data are available for sharing upon reasonable request.

**Dissemination declaration**: We plan to disseminate our results publicly but it would not be feasible to reach discharged patients with study results and therefore we do not plan to contact study participants for dissemination.

**Author Contributions**:

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. David Tong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Transparency statement*: David Tong attests that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

*Concept and design:* All authors

*Acquisition, analysis, or interpretation of data:* All authors

*Drafting of the manuscript:* JO, BT, DT

*Critical revision of the manuscript for important intellectual content:* All authors

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All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. Dr. G. O'Keefe served on an advisory board of Eyepoint Pharmaceuticals in 2019. It is unrelated to the current work.

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**FIGURES**

**Figure 1: Time course of individual symptoms**
Figure 1a: All patients, n=273 (% patients having symptom each day of covid-19 disease)
Figure 1b: Mild provider assessed symptom severity n=164
Figure 1c: Moderate provider assessed symptom severity n=86
Figure 1d: Severe provider assessed symptom severity n=4

**Figure 2: Day of Symptom Onset by System**

**Figure 3: Duration of Symptoms**

**Figure 4: Symptom Duration by Provider Assessed Symptom Severity**

All patients n=273

percentage of patients having the symptom during each day of disease course

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fever | 24 | 27 | 25 | 23 | 21 | 20 | 18 | 17 | 15 | 12 | 10 | 11 | 7 | 4 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |
| Chills | 29 | 38 | 40 | 40 | 36 | 34 | 30 | 26 | 23 | 18 | 15 | 13 | 11 | 8 | 7 | 4 | 3 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 1 |
| Body Aches | 38 | 47 | 52 | 51 | 48 | 42 | 39 | 37 | 35 | 31 | 27 | 26 | 21 | 18 | 16 | 14 | 11 | 7 | 8 | 10 | 9 | 9 | 8 | 8 | 8 | 8 | 7 | 6 | 6 | 5 |
| Dizzy | 8 | 14 | 16 | 18 | 19 | 19 | 18 | 17 | 18 | 18 | 15 | 13 | 11 | 10 | 8 | 7 | 6 | 5 | 4 | 4 | 4 | 4 | 4 | 3 | 3 | 3 | 2 | 1 | 1 | 1 |
| Confusion | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HA | 39 | 48 | 50 | 48 | 49 | 47 | 41 | 38 | 34 | 33 | 28 | 27 | 24 | 22 | 21 | 18 | 16 | 14 | 11 | 11 | 9 | 10 | 11 | 11 | 8 | 7 | 6 | 5 | 5 | 4 |
| Loss of Smell/Taste | 27 | 36 | 41 | 46 | 51 | 54 | 52 | 54 | 54 | 47 | 44 | 38 | 35 | 33 | 29 | 23 | 21 | 18 | 15 | 12 | 14 | 14 | 11 | 10 | 9 | 8 | 7 | 6 | 5 | 5 |
| Congestion | 34 | 40 | 45 | 47 | 47 | 45 | 46 | 44 | 44 | 43 | 40 | 34 | 32 | 29 | 28 | 27 | 25 | 21 | 17 | 15 | 15 | 15 | 11 | 10 | 8 | 7 | 6 | 6 | 5 | 5 |
| Sore Throat | 22 | 24 | 25 | 24 | 21 | 19 | 18 | 17 | 14 | 12 | 12 | 10 | 8 | 10 | 9 | 8 | 8 | 7 | 6 | 4 | 3 | 4 | 3 | 4 | 5 | 4 | 2 | 3 | 2 | 2 |
| Cough | 48 | 55 | 58 | 60 | 62 | 61 | 59 | 61 | 60 | 57 | 51 | 46 | 42 | 40 | 39 | 37 | 34 | 28 | 23 | 21 | 19 | 21 | 17 | 16 | 15 | 13 | 11 | 8 | 8 | 7 |
| Chest Tightness | 14 | 18 | 22 | 24 | 25 | 24 | 25 | 25 | 23 | 21 | 21 | 19 | 16 | 15 | 14 | 12 | 11 | 9 | 7 | 6 | 5 | 5 | 5 | 5 | 4 | 4 | 4 | 4 | 3 | 3 |
| SOB at rest | 5 | 5 | 7 | 10 | 10 | 9 | 10 | 10 | 9 | 6 | 6 | 7 | 5 | 3 | 3 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 |
| SOB with exertion | 15 | 19 | 24 | 26 | 29 | 30 | 33 | 34 | 31 | 32 | 29 | 29 | 27 | 23 | 22 | 23 | 21 | 16 | 14 | 14 | 14 | 13 | 12 | 11 | 10 | 9 | 9 | 7 | 5 | 5 |
| Wheezing | 4 | 5 | 6 | 8 | 10 | 8 | 8 | 8 | 6 | 5 | 4 | 4 | 3 | 3 | 2 | 3 | 1 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 1 | 1 | 1 | 1 |
| Abdominal Pain | 5 | 6 | 7 | 8 | 10 | 11 | 9 | 9 | 8 | 8 | 7 | 6 | 5 | 5 | 5 | 4 | 3 | 2 | 2 | 2 | 3 | 4 | 3 | 3 | 1 | 2 | 2 | 1 | 2 | 1 |
| Nausea | 8 | 10 | 11 | 13 | 15 | 17 | 17 | 16 | 15 | 14 | 14 | 12 | 9 | 9 | 9 | 7 | 3 | 4 | 4 | 4 | 5 | 5 | 4 | 3 | 3 | 2 | 2 | 2 | 1 | 0 |
| Diarrhea | 15 | 18 | 17 | 20 | 23 | 25 | 24 | 24 | 22 | 21 | 22 | 17 | 12 | 12 | 12 | 9 | 8 | 6 | 5 | 5 | 6 | 5 | 4 | 3 | 2 | 3 | 3 | 1 | 1 | 1 |
| Joint Pain | 12 | 15 | 18 | 19 | 22 | 22 | 20 | 17 | 15 | 15 | 16 | 14 | 14 | 11 | 11 | 10 | 9 | 8 | 8 | 7 | 7 | 7 | 6 | 6 | 6 | 5 | 5 | 5 | 4 | 5 |
| Rash | 1 | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 | 2 | 2 |

Moderate n=86

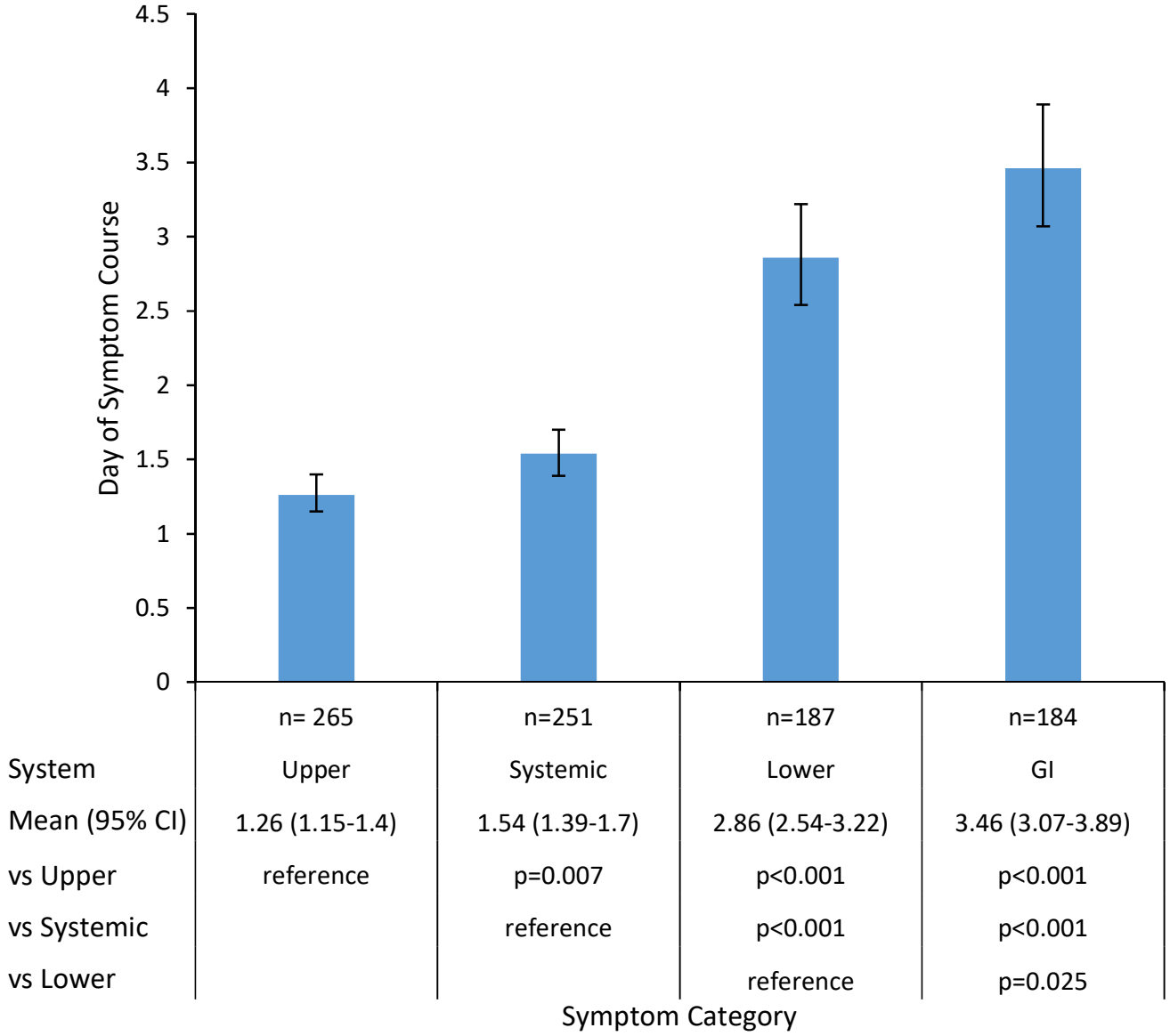
| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fever | 30 | 36 | 33 | 33 | 30 | 30 | 28 | 22 | 19 | 17 | 17 | 19 | 12 | 6 | 5 | 1 | 1 | 1 | 1 | 1 | 2 | 3 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 2 |
| Chills | 30 | 43 | 50 | 53 | 51 | 51 | 49 | 41 | 36 | 29 | 27 | 21 | 17 | 9 | 7 | 3 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 6 | 5 | 3 | 2 | 3 | 3 | 2 |
| Body Aches | 44 | 57 | 66 | 70 | 71 | 65 | 63 | 60 | 57 | 50 | 42 | 35 | 30 | 23 | 24 | 21 | 19 | 14 | 15 | 17 | 15 | 15 | 12 | 12 | 14 | 13 | 13 | 10 | 9 | 9 |
| Dizzy | 13 | 22 | 26 | 28 | 30 | 29 | 34 | 35 | 34 | 29 | 24 | 21 | 17 | 13 | 13 | 9 | 8 | 7 | 6 | 7 | 7 | 7 | 7 | 6 | 5 | 5 | 2 | 1 | 1 | 1 |
| Confusion | 1 | 1 | 1 | 0 | 0 | 0 | 2 | 2 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HA | 44 | 51 | 57 | 57 | 57 | 52 | 51 | 51 | 48 | 47 | 38 | 37 | 38 | 35 | 31 | 24 | 26 | 23 | 19 | 20 | 15 | 15 | 15 | 16 | 13 | 10 | 8 | 8 | 7 | 7 |
| Loss of Smell/Taste | 24 | 38 | 44 | 50 | 52 | 56 | 58 | 63 | 60 | 50 | 49 | 45 | 44 | 42 | 35 | 30 | 27 | 28 | 21 | 17 | 22 | 21 | 16 | 13 | 10 | 10 | 10 | 10 | 8 | 7 |
| Congestion | 30 | 37 | 41 | 42 | 47 | 43 | 51 | 50 | 55 | 51 | 44 | 40 | 37 | 40 | 38 | 36 | 37 | 34 | 30 | 29 | 28 | 30 | 19 | 20 | 16 | 15 | 13 | 13 | 10 | 10 |
| Sore Throat | 22 | 23 | 24 | 24 | 23 | 21 | 21 | 19 | 16 | 12 | 10 | 6 | 7 | 12 | 13 | 12 | 9 | 8 | 6 | 5 | 5 | 6 | 5 | 9 | 10 | 7 | 6 | 6 | 3 | 2 |
| Cough | 56 | 65 | 71 | 72 | 74 | 70 | 71 | 74 | 74 | 71 | 59 | 62 | 59 | 56 | 56 | 55 | 51 | 40 | 35 | 36 | 33 | 33 | 27 | 26 | 26 | 19 | 16 | 12 | 12 | 12 |
| Chest Tightness | 14 | 21 | 30 | 33 | 31 | 30 | 37 | 36 | 35 | 28 | 22 | 20 | 19 | 20 | 16 | 15 | 12 | 8 | 8 | 6 | 8 | 8 | 8 | 10 | 8 | 8 | 8 | 8 | 5 | 7 |
| SOB at rest | 7 | 7 | 9 | 15 | 16 | 13 | 19 | 15 | 13 | 8 | 8 | 8 | 6 | 3 | 5 | 5 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 2 | 1 | 3 | 3 | 2 | 1 | 1 |
| SOB with exertion | 27 | 33 | 40 | 43 | 48 | 48 | 51 | 53 | 50 | 51 | 47 | 44 | 42 | 36 | 35 | 31 | 35 | 24 | 22 | 23 | 23 | 21 | 21 | 19 | 13 | 13 | 14 | 10 | 6 | 6 |
| Wheezing | 6 | 9 | 13 | 16 | 17 | 14 | 17 | 19 | 13 | 10 | 7 | 6 | 5 | 5 | 2 | 3 | 2 | 2 | 1 | 1 | 3 | 3 | 5 | 2 | 0 | 0 | 1 | 1 | 0 | 1 |
| Abdominal Pain | 7 | 10 | 15 | 13 | 15 | 16 | 15 | 15 | 13 | 10 | 10 | 9 | 8 | 9 | 6 | 6 | 6 | 5 | 6 | 6 | 6 | 9 | 7 | 6 | 5 | 3 | 3 | 2 | 5 | 3 |
| Nausea | 16 | 17 | 21 | 20 | 22 | 26 | 27 | 26 | 23 | 22 | 19 | 16 | 14 | 14 | 14 | 12 | 6 | 7 | 7 | 9 | 10 | 9 | 8 | 8 | 6 | 5 | 3 | 3 | 3 | 0 |
| Diarrhea | 21 | 27 | 30 | 35 | 36 | 42 | 41 | 37 | 37 | 34 | 31 | 26 | 20 | 16 | 16 | 16 | 16 | 14 | 12 | 13 | 13 | 10 | 8 | 7 | 7 | 6 | 5 | 3 | 2 | 1 |
| Joint Pain | 17 | 24 | 31 | 33 | 36 | 35 | 36 | 34 | 30 | 28 | 26 | 26 | 24 | 15 | 19 | 16 | 19 | 16 | 16 | 13 | 9 | 9 | 7 | 8 | 10 | 8 | 9 | 9 | 8 | 10 |
| Rash | 2 | 2 | 3 | 3 | 3 | 2 | 3 | 3 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 2 | 3 | 2 | 2 | 2 | 0 | 0 | 0 | 1 | 1 |

Mild n=164

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fever | 21 | 24 | 22 | 18 | 16 | 15 | 14 | 15 | 14 | 10 | 7 | 7 | 5 | 4 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 |
| Chills | 27 | 34 | 32 | 30 | 27 | 24 | 20 | 17 | 14 | 10 | 7 | 7 | 5 | 5 | 5 | 2 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 1 |
| Body Aches | 35 | 41 | 46 | 42 | 36 | 30 | 27 | 24 | 24 | 21 | 20 | 21 | 15 | 13 | 10 | 9 | 6 | 3 | 3 | 5 | 5 | 5 | 5 | 4 | 3 | 4 | 3 | 3 | 3 | 3 |
| Dizzy | 4 | 10 | 11 | 13 | 14 | 14 | 11 | 8 | 9 | 11 | 10 | 8 | 7 | 7 | 4 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Confusion | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HA | 35 | 46 | 46 | 43 | 45 | 43 | 35 | 30 | 25 | 26 | 22 | 22 | 16 | 15 | 13 | 15 | 12 | 10 | 8 | 7 | 5 | 7 | 9 | 8 | 5 | 5 | 5 | 3 | 3 | 2 |
| Loss of Smell/Taste | 27 | 33 | 41 | 43 | 49 | 52 | 51 | 49 | 49 | 45 | 41 | 34 | 30 | 28 | 25 | 19 | 18 | 13 | 11 | 9 | 10 | 10 | 9 | 8 | 7 | 7 | 4 | 4 | 4 | 4 |
| Congestion | 35 | 41 | 45 | 47 | 45 | 45 | 41 | 38 | 38 | 37 | 38 | 31 | 28 | 24 | 23 | 22 | 18 | 14 | 10 | 8 | 7 | 8 | 7 | 6 | 4 | 4 | 3 | 3 | 3 | 2 |
| Sore Throat | 21 | 24 | 24 | 23 | 19 | 18 | 16 | 15 | 13 | 11 | 12 | 10 | 9 | 9 | 6 | 5 | 5 | 5 | 4 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 |
| Cough | 42 | 49 | 51 | 53 | 54 | 54 | 52 | 54 | 52 | 51 | 46 | 38 | 33 | 32 | 29 | 26 | 24 | 21 | 16 | 13 | 12 | 15 | 12 | 10 | 9 | 8 | 7 | 5 | 4 | 3 |
| Chest Tightness | 11 | 14 | 15 | 18 | 18 | 19 | 16 | 16 | 15 | 15 | 17 | 16 | 13 | 11 | 10 | 8 | 7 | 7 | 5 | 4 | 4 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 |
| SOB at rest | 4 | 4 | 5 | 7 | 6 | 7 | 4 | 6 | 7 | 5 | 4 | 7 | 5 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 |
| SOB with exertion | 7 | 10 | 13 | 14 | 16 | 18 | 21 | 22 | 18 | 19 | 19 | 19 | 18 | 15 | 13 | 15 | 12 | 9 | 7 | 7 | 8 | 8 | 7 | 6 | 7 | 6 | 5 | 3 | 2 | 2 |
| Wheezing | 2 | 2 | 2 | 3 | 5 | 5 | 4 | 3 | 4 | 3 | 4 | 4 | 3 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 |
| Abdominal Pain | 4 | 5 | 4 | 7 | 8 | 9 | 7 | 7 | 7 | 7 | 7 | 4 | 4 | 4 | 4 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 |
| Nausea | 4 | 5 | 6 | 9 | 12 | 13 | 12 | 12 | 11 | 10 | 11 | 9 | 6 | 5 | 7 | 4 | 1 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 1 |
| Diarrhea | 13 | 15 | 12 | 14 | 17 | 17 | 17 | 18 | 15 | 16 | 18 | 12 | 8 | 11 | 10 | 5 | 4 | 2 | 1 | 1 | 2 | 2 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 |
| Joint Pain | 9 | 11 | 12 | 13 | 15 | 15 | 12 | 9 | 9 | 9 | 12 | 9 | 10 | 9 | 8 | 7 | 4 | 3 | 4 | 5 | 4 | 5 | 5 | 4 | 2 | 3 | 3 | 3 | 3 | 3 |
| Rash | 1 | 2 | 2 | 2 | 3 | 3 | 3 | 2 | 2 | 2 | 2 | 2 | 2 | 4 | 4 | 3 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 2 |

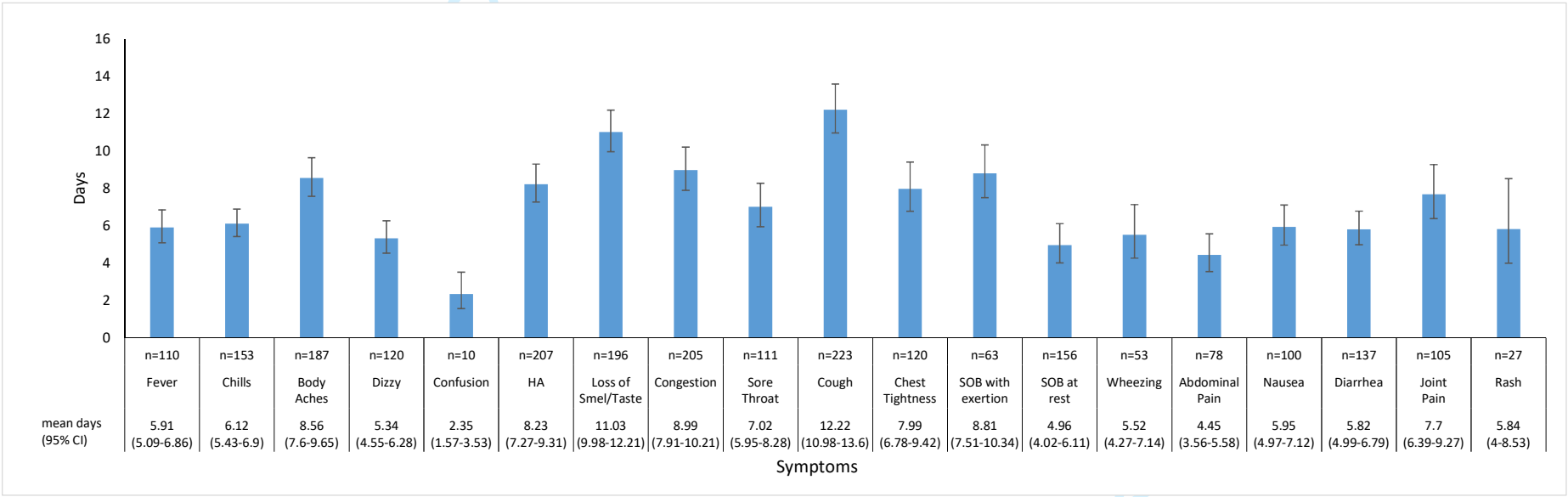
Severe n=4

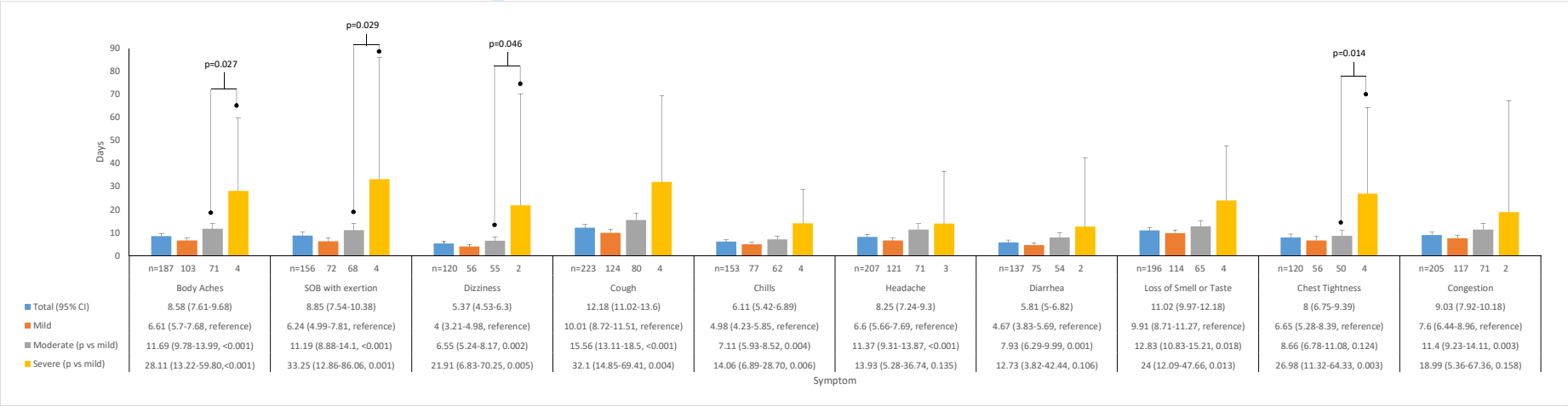
| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fever | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chills | 75 | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 50 | 25 | 25 | 25 | 0 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Body Aches | 75 | 75 | 75 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 100 | 100 | 75 | 50 | 50 | 75 | 50 | 25 | 50 | 50 | 75 | 75 | 50 | 50 | 50 | 50 | 50 |
| Dizzy | 25 | 25 | 25 | 25 | 25 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 0 |
| Confusion | 0 | 0 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| HA | 50 | 75 | 75 | 75 | 75 | 75 | 75 | 50 | 50 | 50 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Loss of Smell/Taste | 50 | 50 | 50 | 75 | 75 | 100 | 75 | 75 | 75 | 100 | 100 | 75 | 100 | 100 | 100 | 100 | 50 | 25 | 50 | 25 | 25 | 25 | 25 | 50 | 75 | 75 | 50 | 25 | 25 | 25 |
| Congestion | 25 | 25 | 25 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 25 | 25 | 25 | 0 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Sore Throat | 50 | 50 | 50 | 50 | 75 | 75 | 75 | 75 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 25 | 0 | 25 | 0 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 25 | 50 | 50 |
| Cough | 75 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 50 | 50 | 50 | 50 | 75 | 100 | 100 | 75 | 75 | 75 | 75 |
| Chest Tightness | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 75 | 100 | 75 | 75 | 50 | 50 | 25 | 25 | 25 | 25 | 75 | 75 | 50 | 50 | 50 | 50 |
| SOB at rest | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 50 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| SOB with exertion | 75 | 75 | 75 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 75 | 50 | 50 | 50 | 75 | 100 | 100 | 100 | 100 | 100 | 100 |
| Wheezing | 25 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 0 | 0 | 25 | 25 | 25 |
| Abdominal Pain | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nausea | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 |
| Diarrhea | 0 | 0 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 0 | 25 | 25 | 0 | 25 | 25 |
| Joint Pain | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 50 | 50 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 50 | 50 | 50 | 25 | 0 | 0 | 0 | 0 | 0 |
| Rash | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 50 | 50 | 25 |




| | | | | |
|---|---|---|---|---|
| | n= 265 | n=251 | n=187 | n=184 |
| System | Upper | Systemic | Lower | GI |
| Mean (95% CI) | 1.26 (1.15-1.4) | 1.54 (1.39-1.7) | 2.86 (2.54-3.22) | 3.46 (3.07-3.89) |
| vs Upper | reference | p=0.007 | p<0.001 | p<0.001 |
| vs Systemic | | reference | p<0.001 | p<0.001 |
| vs Lower | | | reference | p=0.025 |

Symptom Category


Days
16
14
12
10
8
6
4
2
0
n=110 Fever 5.91 (5.09-6.86)
n=153 Chills 6.12 (5.43-6.9)
n=187 Body Aches 8.56 (7.6-9.65)
n=120 Dizzy 5.34 (4.55-6.28)
n=10 Confusion 2.35 (1.57-3.53)
n=207 HA 8.23 (7.27-9.31)
n=196 Loss of Smel/Taste 11.03 (9.98-12.21)
n=205 Congestion 8.99 (7.91-10.21)
n=111 Sore Throat 7.02 (5.95-8.28)
n=223 Cough 12.22 (10.98-13.6)
n=120 Chest Tightness 7.99 (6.78-9.42)
n=63 SOB with exertion 8.81 (7.51-10.34)
n=156 SOB at rest 4.96 (4.02-6.11)
n=53 Wheezing 5.52 (4.27-7.14)
n=78 Abdominal Pain 4.45 (3.56-5.58)
n=100 Nausea 5.95 (4.97-7.12)
n=137 Diarrhea 5.82 (4.99-6.79)
n=105 Joint Pain 7.7 (6.39-9.27)
n=27 Rash 5.84 (4-8.53)
mean days (95% CI)
Symptoms


p=0.027
p=0.029
p=0.046
p=0.014
Days
90
80
70
60
50
40
30
20
10
0
Body Aches
SOB with exertion
Dizziness
Cough
Chills
Headache
Diarrhea
Loss of Smell or Taste
Chest Tightness
Congestion
Symptom
Total (95% CI)
Mild
Moderate (p vs mild)
Severe (p vs mild)
n=187 103 71 4
8.58 (7.61-9.68)
6.61 (5.7-7.68, reference)
11.69 (9.78-13.99, <0.001)
28.11 (13.22-59.80,<0.001)
n=156 72 68 4
8.85 (7.54-10.38)
6.24 (4.99-7.81, reference)
11.19 (8.88-14.1, <0.001)
33.25 (12.86-86.06, 0.001)
n=120 56 55 2
5.37 (4.53-6.3)
4 (3.21-4.98, reference)
6.55 (5.24-8.17, 0.002)
21.91 (6.83-70.25, 0.005)
n=223 124 80 4
12.18 (11.02-13.6)
10.01 (8.72-11.51, reference)
15.56 (13.11-18.5, <0.001)
32.1 (14.85-69.41, 0.004)
n=153 77 62 4
6.11 (5.42-6.89)
4.98 (4.23-5.85, reference)
7.11 (5.93-8.52, 0.004)
14.06 (6.89-28.70, 0.006)
n=207 121 71 3
8.25 (7.24-9.3)
6.6 (5.66-7.69, reference)
11.37 (9.31-13.87, <0.001)
13.93 (5.28-36.74, 0.135)
n=137 75 54 2
5.81 (5-6.82)
4.67 (3.83-5.69, reference)
7.93 (6.29-9.99, 0.001)
12.73 (3.82-42.44, 0.106)
n=196 114 65 4
11.02 (9.97-12.18)
9.91 (8.71-11.27, reference)
12.83 (10.83-15.21, 0.018)
24 (12.09-47.66, 0.013)
n=120 56 50 4
8 (6.75-9.39)
6.65 (5.28-8.39, reference)
8.66 (6.78-11.08, 0.124)
26.98 (11.32-64.33, 0.003)
n=205 117 71 2
9.03 (7.92-10.18)
7.6 (6.44-8.96, reference)
11.4 (9.23-14.11, 0.003)
18.99 (5.36-67.36, 0.158)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract<br>(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1-2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4-5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>(*b*) For matched studies, give matching criteria and number of exposed and unexposed | 6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-10 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8-9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 10 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding<br>(*b*) Describe any methods used to examine subgroups and interactions<br>(*c*) Explain how missing data were addressed<br>(*d*) If applicable, explain how loss to follow-up was addressed<br>(*e*) Describe any sensitivity analyses | 10-11 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram | 12 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) Summarise follow-up time (eg, average and total amount) | 12-14 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 14-16 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 16 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 17-18 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 19-20 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 18-19 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 20 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | NA |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# Predictors of disease duration and symptom course of outpatients with acute covid-19: a retrospective cohort study



| | |
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| | |

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**Title:** Predictors of disease duration and symptom course of outpatients with acute covid-19: a retrospective cohort study

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## ABSTRACT

**Objective:** Describe the disease course in a cohort of outpatients with covid-19 and evaluate factors predicting duration of symptoms

**Design:** Retrospective cohort study

**Setting:** Telemedicine clinic at a large medical system in Atlanta, Georgia

**Participants:** 340 patients with COVID-19. Exclusion criteria included intake more than 10 days after symptom onset.

**Main outcome measures:** Symptom duration in days

**Results:** Common symptoms at intake visit are upper respiratory (74% cough, 55% loss of smell or taste, 57% sinus congestion, 32% sore throat), systemic (65% headache, 64% body aches, 53% chills, 30% dizziness, 36% fever). Day of symptom onset was earliest for systemic and upper respiratory symptoms (median onset day 1 for both), followed by lower respiratory symptoms (day 3, 95% CI 2-4), with later onset of gastrointestinal symptoms (day 4, 3 to 5), when present. Cough had the longest duration when present with median 17 days (15 to 21), with 42% not resolved at final visit. Loss of smell or taste had the second longest duration with 14 days (12 to 17), with 38% not resolved at final visit. Initial symptom severity is the best predictor of symptom duration ($p<0.01$ for multiple symptoms).

**Conclusions:** Covid-19 illness in outpatients follows a pattern of progression from systemic symptoms to lower respiratory symptoms and persistent symptoms are common across categories. Initial symptom severity is the best predictor of disease duration.

## Strengths and limitations of this study

Strengths:

- By systematically calling patients throughout acute illness, we are able to provide a visual representation of symptoms of acute illness in outpatients.
- Missing data are minimal during acute illness as patients are followed until symptom improvement.
- We used standardized templates for all patients and are able to analyze predictors of symptom duration for specific variables including age, comorbidities and symptom severity.

Limitations

- We are a single center study with limited patient numbers.
- We do not follow patients until disease resolution and cannot define an end date for all symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Covid-19 symptoms in non-hospitalized adults span multiple organ systems, most often including respiratory and systemic symptoms

Symptom duration varies substantially between patients, ranging from brief (days) to prolonged (weeks to months)

WHAT THIS STUDY ADDS

Disease duration is predicted by the severity of initial symptoms during the acute illness

Disease course can be described in a pattern with early systemic symptoms, followed by lower respiratory and, less often, gastrointestinal symptoms

Multiple symptoms may persist to 30 days, most often cough, loss of smell or taste, sinus congestion, shortness of breath on exertion, body aches, and headache

## INTRODUCTION

Coronavirus disease 2019 (covid-19) has brought large numbers of patients to medical attention within a span of months for care of a previously undescribed illness. Early reports on the presentation and natural history of covid-19 appropriately focused attention on the severe cases and critically ill.[1-5] Subsequent surveillance has demonstrated that the majority of patients have milder forms of illness [6] and it is recommended that they remain at home with medical supervision.[7,8] Although the duration of home isolation is defined based on symptoms,[7] understanding of the symptom course of outpatients with covid-19 is limited and most reports include presenting symptoms alone or cross-sectional follow-up information.[9-17] Longitudinal symptom data and predictors of individual symptom duration have not been described.

In March 2020, we established a virtual clinic for the care of patients in home isolation with covid-19: the “Virtual Outpatient Management Clinic” (VOMC), using available knowledge for assessment and treatment guidelines. All patients underwent VOMC intake visits with a physician or advanced practice provider (APP), including assessment of specific covid-19 symptoms using a standardized clinical note. Patients were followed for symptom management with regular telephone calls by registered nurses (RNs) and APPs until improvement or hospitalization. Subsets from this cohort have been reported elsewhere in a small case series[18] and for hospitalization risk prediction;[19] the current study is the first to analyze complete longitudinal symptom reporting for the cohort.

As it became clear in clinical practice that symptom duration varies substantially between patients, we undertook this study to determine the predictors of the symptom course of our VOMC cohort. We hypothesized that a combination of demographics, comorbidities, and initial symptom severity would predict symptom duration.

## METHODS

### Study setting

The study was a retrospective cohort study, conducted at Emory Healthcare, the largest academic health system in Georgia (serving the greater Atlanta metropolitan area), which includes more than 250 provider locations and 120 primary care locations. The VOMC comprised an intake team of 14 physicians and 3 APPs from two primary care clinics; and follow-up call teams included 19 redeployed registered nurses (RNs) and 20 APPs. All intake providers were trained in the use of the risk assessment tool in a one-hour webinar and conducted a median of 25 intake visits during the study period (range: 5-99), with the majority of intake visits conducted by physicians (83.6%).

### Study cohort

We included outpatient adults who completed their VOMC intake visit between 24 March 2020 and 26 May 2020 with initial symptom dates between 17 March and 20 May. We excluded patients with an intake visit more than 10 days after symptom onset in order to improve the accuracy of early symptom reporting.

During the study period, outpatient covid-19 testing was conducted by medical providers using nasopharyngeal sampling for real-time reverse transcription–polymerase chain reaction (RT-PCR) detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Adult patients with positive RT-PCR results from the screening clinics or emergency departments (EDs) were called by a result notification team to provide self-care advice and refer for enrollment in the VOMC. The criteria for testing and details of care are outlined in Box 1. Symptom severity was assessed both by the provider using criteria in Box 1 as well as self-reported by the patient.

BOX 1: Virtual Outpatient Management Clinic (VOMC) Care

**Outpatient covid-19 testing (March-April 2020):**

1. Symptom(s): either (a) fever, cough, or shortness of breath or (b) two symptoms from the following: sore throat, congestion, myalgias, fatigue, diarrhea, loss of smell.
2. Prioritize: (a) frontline healthcare workers, (b) students on-campus and health professions, (c) CDC employees, (d) patients with risk factors (age, comorbidity, immunosuppression, work in a communal setting).
3. Setting: outpatient clinic repurposed as testing site (12 March 2020) and additional drive-through site added to expand capacity (9 April 2020).

**Emergency Department covid-19 testing (March 2020):**

1. Symptom(s): cough, fever, sore throat, or shortness of breath.
2. Prioritize: (a) severe illness (difficulty breathing or other indication for admission), (b) high risk comorbidities including chronic lung disease, heart disease, chronic kidney disease, diabetes, immunocompromising conditions, or (c) communal housing or living with high-risk individual.

**VOMC enrollment criteria:**

1. Diagnosis of covid-19 by nasopharyngeal PCR, and
2. Requesting* outpatient monitoring and/or management of covid-19 symptoms.

*All patients with positive results were notified by telephone and offered VOMC referral.

**Intake VOMC visit:**

1. Documentation template includes symptom history, symptom severity (patient-reported and provider-assessed), past medical history, physical examination and risk assessment.
2. Symptoms assessed: “systemic” (fever, chills, body aches, dizziness, headache, joint pain), “upper respiratory” (loss of smell or taste, sinus congestion, sore throat, cough), “lower respiratory” (chest tightness, shortness of breath with exertion, shortness of breath at rest, wheezing), “gastrointestinal” (abdominal pain, nausea, diarrhea), as well as confusion and rash. Note: symptoms assessed as a single list and not grouped into categories during assessment.
3. Provider gives advice for (1) symptom management, (2) home isolation guidance and (3) outpatient monitoring.

**Provider-assessed symptom severity definition:**

1. Mild
    a. Respiratory: Cough, sputum production
    b. Systemic: Fever, chills, malaise, myalgia, anorexia, diarrhea, vomiting, headache
2. Moderate
    a. Respiratory: Severe cough, dyspnea on exertion, wheezing or sensation of mid-chest tightness

b. Systemic: N/A (Not provided in VOMC clinical guideline)

3. Severe

a. Resting dyspnea, labored breathing, resting pulse oximetry ≤92%, pleuritic pain, hemoptysis

b. Systemic: acute confusion, severe weakness, syncope, acute decline in functional status

**Follow-up phone calls (March-June 2020):**

1. Patients receive VOMC follow-up telephone calls based on hospitalization risk tool[19] that includes age, comorbidity, symptom severity, and social support:
   a. Low risk: every other day for a minimum of 7 days from symptom onset
   b. Intermediate risk: daily for a minimum of 14 days from symptom onset
   c. High risk: twice daily for a minimum of 21 days from symptom onset
2. All patients called until the intervals above and for a minimum 3 days after improvement in fevers (without antipyretics) and improvement in respiratory symptoms (whichever criteria was longer).
3. Patients with improving or worsening symptoms could change risk level after enrollment at provider discretion.

## Data sources

Study data were obtained from two specific provider note types deployed in March 2020 within the Emory Healthcare electronic health record (Cerner Corp., Kansas City, Missouri, United States): (1) VOMC provider intake visit and (2) VOMC follow-up telephone call. The intake visit assessment note template included (1) documentation of specific covid-19 symptoms including onset and offset dates, (2) patient reported and provider-assessed symptom severity, and (3) documentation of specific medical conditions associated with risk of severe covid-19 (based on medical literature search in March 2020). The VOMC follow-up telephone call template included an identical symptom list with “yes/no” selection for documentation of the presence or absence of symptoms at follow-up.

If symptom onset date was not identified in VOMC notes, we conducted manual chart review of telephone records prior to VOMC enrollment. Additional demographic

information including age, gender, and race (if recorded) was included from the electronic health record.

To ensure that symptoms were counted only once a day per patient, among patients receiving 2 calls per day, if a symptom was listed as present more than once for a particular day, it was counted only once. Among patients receiving calls every other day, if a symptom was present on both the preceding and subsequent day it was listed as present on the single non-call day in between for symptom duration.

**Main outcomes**

To create a visual representation of overall disease as a heatmap, we define day 1 as the first day a patient had any symptom and each individual symptom is counted only on days present.

The main outcome was duration in days for each specific symptom, using the first and last documented dates a symptom was present. Because patients could be discharged from VOMC with ongoing symptoms, if a symptom was present on the last nurse phone call it was considered censored for survival analysis. If a symptom was not present on the last nurse phone call then the symptom was considered resolved.

The secondary outcome was the day of symptom onset. Symptoms were grouped into systems: upper respiratory (cough, congestion, sore throat, loss of smell or taste),

systemic (fever, body aches, chills, dizziness, headache, joint pain), lower respiratory (shortness of breath with exertion, shortness of breath at rest, chest tightness, wheezing) and gastrointestinal (nausea, abdominal pain, diarrhea). Confusion and rash were not included into symptom groups. For initial symptom severity, we used the provider-assessed severity at the intake visit (criteria in Box 1). If provider-assessed severity was not available (n=25) then the patient-reported severity at intake visit was used (n=18 mild and n=7 moderate). Clinical record extraction was conducted 21 June 2020 at which time all enrolled patients had at least 30 days of follow up based on symptom start date and all patients had received their final VOMC nurse call.

**Bias**

Screening criteria are noted in Box 1. Healthcare employees were prioritized in the outpatient screening process and may be overrepresented in the cohort. Screening in the emergency room prioritized patients with more severe symptoms and likely underrepresented mild disease. Patient enrollment in VOMC was voluntary at the time of results notification, which may also result in selection bias for more symptomatic patients. Patients were scheduled for the minimum recommended follow-up calls at the time of intake (and could later extend care further if needed) but could disengage on request, which could lead to attrition bias.

**Predictors**

Demographics, comorbidities, and initial symptom severity were tested as predictors of symptom duration.

**Statistical analysis**

Survival analysis was used to analyze symptom start date by system and duration of individual symptoms. Kaplan-Meier curves were constructed for symptom onset (grouped by systems) to calculate median day of onset, and for median duration of symptoms. Pairwise log-rank test was used to compare the system groupings. Kaplan-Meier curves were also used to determine the median duration for each symptom. Cox proportional hazard models were constructed but the proportional hazards requirement was not met for several covariate symptom combinations so Cox models were not used. Time-varying covariates can be included as strata but different baseline hazards are modeled for each strata so the effect of the strata covariate is not estimated.[20] Time-by-covariate interactions can be incorporated into the models but would be hard to interpret (supplement table 1).

Subsequent analysis showed accelerated failure time (AFT) models had a better fit. AFT models are an alternate method of survival analysis which is parametric and does not require proportional hazards. To decrease the chance of false positive findings we screened each comorbidity to see if it was a significant predictor of symptom duration with symptom duration analyzed as strata (supplement table 2). Models were developed for each symptom including only the covariates that were significant (gender, initial symptom severity, race, asthma, immunosuppression, obesity) to the $p<0.001$ level. Statistically significant covariates for each symptom's model were retained in the final AFT models. The Akaike information criterion (AIC) showed the AFT models were a

better fit than the Cox proportional hazards models (supplement table 3). Log-normal and log-logistic distribution AFT models appeared to fit the data the best with very similar results (supplement table 4), and we present the log-logistic distribution model in this paper with projected survival curves for different models in supplement figure 1. Goodness-of-fit testing was performed for the log-normal and log-logistic AFT models (supplement figure 2a and 2b). Self-reported symptom severity was used if provider-assessed symptom severity was missing (n=25). This resulted in a similar goodness of fit compared to imputing the missing provider assessed severity (supplement table 5). Statistical analysis was performed using RStudio version 4.0.3 packages survival and flexsurv (R core Team, 2020).

**Patient and public involvement**

Patients and the public were not involved in the design and conduct of the study, outcomes, recruitment, or planned dissemination.

**RESULTS:**

551 intake visits were completed in VOMC between 24 March 2020 and 26 May 2020. We included 340 patients in the study after excluding: 198 patients with VOMC intake visit more than 10 days after symptom onset, 6 patients without documented positive RT-PCR test for SARS-CoV-2, 3 patients with blank or uninterpretable symptom entries and 1 patient with neither provider or self-reported initial symptom severity. Of the included hospitalized patients, 33 were seen initially in VOMC (before hospitalization) and 3 patients were hospitalized prior to being seen in VOMC (with 2 readmitted during

the time of VOMC care). Nine of the hospitalized patients resumed VOMC care after hospital discharge.

The testing location for included patients was primarily outpatient (n=304, 89%), followed by ED (n=34, 10%), and 2 patients tested as inpatients (1%). During the study period (testing dates 15 March 2020 to 22 May 2020), the following number of patients were tested at Emory Healthcare: 730 in the outpatient setting, 170 in the ED, 740 in the inpatient setting, 1 in ambulatory surgery and 1 patient in hospice.

**Characteristics of the study population**

Table 1 describes demographics, comorbidities, and symptoms recorded at the VOMC intake visit for the cohort grouped by initial symptom severity. Our study population had a mean age of 45.6 years, 68% women, and 52% black. The mean number of days from symptom onset to VOMC intake visit was 5.8 days, with follow-up phone calls continuing until mean symptom day 19. There was a significant difference in the initial symptom severity by patient age. Asthma, heart failure, hypertension, and diabetes were significantly different ($P<0.05$) between the initial symptom severity groups. Only eight patients had severe initial symptoms severity and four (50%) were hospitalized during care. Of the four nonhospitalized patients in the severe symptom group, two were evaluated by the in-person covid-19 clinic and determined to be stable for outpatient monitoring and two were managed by the VOMC telemedicine team alone without escalation to in-person care.

## Table 1 Demographics, comorbidities and symptoms at VOMC intake visit

| | Initial Symptom Severity | | | | Anova p value |
|---|---|---|---|---|---|
| Demographics: | Total (n=340) | mild (n=225) | moderate (n=107) | severe (n=8) | |
| Age, mean (95% CI) | 45.6 (44.1-47.2) | 43.9 (42.0-45.7) | 48.3 (45.6-51.1) | 57.9 (44.8-71.0) | <0.001 |
| Symptom onset to intake VOMC visit (days, 95% CI) | 5.8 (5.5-6.0) | 5.6 (5.3-6.0) | 6.0 (5.6-6.4) | 5.6 (4.1-7.1) | 0.309 |
| Symptom onset to last phone call (days, 95% CI) | 19.0 (17.9-20.0) | 17.2 (16.1-18.3) | 22.7 (20.6-24.7) | 19.9 (6.3-33.5) | <0.001 |
| Count, (%) | | | | | $Chi^2$ p value |
| Gender, Men | 108 (32%) | 74 (33%) | 34 (32%) | 0 (0%) | 0.146 |
| Gender, Women | 232 (68%) | 151 (67%) | 73 (68%) | 8 (100%) | |
| Race, White | 59 (17%) | 38 (17%) | 19 (18%) | 2 (25%) | 0.403 |
| Race, Black | 177 (52%) | 114 (51%) | 57 (53%) | 6 (75%) | |
| Race, Other/Unknown | 104 (31%) | 73 (32%) | 31 (29%) | 0 (0%) | |
| Co-morbidities: | | | | | |
| Age>=60 | 62 (18%) | 35 (16%) | 25 (23%) | 2 (25%) | 0.200 |
| Alcohol abuse/addiction | 4 (1%) | 2 (1%) | 2 (2%) | 0 (0%) | 0.706 |
| Asthma | 43 (13%) | 19 (8%) | 22 (21%) | 2 (25%) | 0.005 |
| Cancer or malignancy | 24 (7%) | 17 (8%) | 6 (6%) | 1 (13%) | 0.674 |
| Confirmed Pregnant | 1 (0.3%) | 1 (0.4%) | 0 (0%) | 0 (0%) | 0.774 |
| COPD | 2 (1%) | 0 (0%) | 2 (2%) | 0 (0%) | 0.112 |
| Coronary artery disease | 9 (3%) | 5 (2%) | 4 (4%) | 0 (0%) | 0.647 |
| Diabetes | 49 (14%) | 26 (12%) | 20 (19%) | 3 (38%) | 0.038 |
| Drug abuse/addiction | 3 (1%) | 2 (1%) | 1 (1%) | 0 (0%) | 0.963 |
| Heart failure | 3 (1%) | 1 (0.4%) | 1 (1%) | 1 (13%) | 0.002 |
| Hypertension | 111 (33%) | 64 (28%) | 41 (38%) | 6 (75%) | 0.007 |
| Immune suppression | 19 (6%) | 9 (4%) | 9 (8%) | 1 (13%) | 0.181 |
| Lung disease | 8 (2%) | 3 (1%) | 5 (5%) | 0 (0%) | 0.156 |
| Obesity (BMI > 30) | 101 (30%) | 60 (27%) | 37 (35%) | 4 (50%) | 0.150 |
| Renal disease | 8 (2%) | 5 (2%) | 3 (3%) | 0 (0%) | 0.859 |
| Symptom present prior to or at intake visit | | | | | |
| current fever | 121 (36%) | 67 (30%) | 51 (48%) | 3 (38%) | 0.004 |
| chills | 181 (53%) | 103 (46%) | 72 (67%) | 6 (75%) | 0.001 |
| body aches | 217 (64%) | 128 (57%) | 83 (78%) | 6 (75%) | 0.001 |
| dizziness when standing | 103 (30%) | 48 (21%) | 51 (48%) | 4 (50%) | <0.001 |
| confusion | 10 (3%) | 4 (2%) | 4 (4%) | 2 (25%) | 0.001 |
| headache | 222 (65%) | 142 (63%) | 74 (69%) | 6 (75%) | 0.470 |
| loss of smell or taste | 188 (55%) | 114 (51%) | 67 (63%) | 7 (88%) | 0.022 |
| sinus congestion | 193 (57%) | 123 (55%) | 65 (61%) | 5 (63%) | 0.548 |
| sore throat | 109 (32%) | 71 (32%) | 35 (33%) | 3 (38%) | 0.925 |

| | | | | | |
|---|---|---|---|---|---|
| cough | 250 (74%) | 151 (67%) | 92 (86%) | 7 (88%) | 0.001 |
| chest tightness | 111 (33%) | 55 (24%) | 50 (47%) | 6 (75%) | <0.001 |
| SOB at rest | 47 (14%) | 19 (8%) | 23 (21%) | 5 (63%) | <0.001 |
| SOB with exertion | 125 (37%) | 50 (22%) | 69 (64%) | 6 (75%) | <0.001 |
| wheezing | 44 (13%) | 21 (9%) | 22 (21%) | 1 (13%) | 0.0173 |
| abdominal pain | 54 (16%) | 28 (12%) | 25 (23%) | 1 (13%) | 0.038 |
| nausea | 84 (25%) | 33 (15%) | 46 (43%) | 5 (63%) | <0.001 |
| diarrhea | 113 (33%) | 63 (28%) | 48 (45%) | 2 (25%) | 0.008 |
| joint pain | 95 (28%) | 45 (20%) | 47 (44%) | 3 (38%) | <0.001 |
| rash | 13 (4%) | 6 (3%) | 6 (6%) | 1 (13%) | 0.184 |

COPD=Chronic Obstructive Pulmonary Disease, SOB=Shortness of Breath

**Symptoms at VOMC intake visit**

The most frequently reported symptoms occurring prior to and at the time of the VOMC intake visit included: 74% cough, 65% headache, 64% body aches, 57% sinus congestion, 55% loss of smell or taste, and 53% chills (table 1). All symptoms within the systemic, lower respiratory, and gastrointestinal systems were significantly different between severity groups. The only symptoms that were not significant were headache, sinus congestion, sore throat, and rash.

**Time course of individual symptoms**

Figure 1 displays heat maps of symptoms for 305 patients, presenting the daily percentage of patients with specified symptoms over a 30 day follow up period. The 35 patients hospitalized after VOMC intake are not included in figure 1 because daily symptom data were not collected during hospitalizations. Among symptoms included in this visual, the highest daily prevalence reported during 30 days of follow up was for cough (60%), loss of smell or taste (50%), body aches (45%), headache (45%), and sinus congestion (45%). The most frequent remaining symptoms at 30 days were

cough (5%), body aches (4%), sinus congestion (3%), and shortness of breath with exertion (3%). Fever was not a prominent symptom during 30 days of follow up, with peak daily prevalence of 22% in the first two days of illness.

**Time course of symptoms by initial symptom severity**

The heat map findings for mild initial symptom severity group (n=210 for heat map) demonstrate similar rates of initial upper respiratory symptoms compared to the entire heat map cohort, with peak daily prevalence of cough in 52% and sinus congestion in 45% during the first week (figure 1). Rates of lower respiratory symptoms were lower (e.g. shortness of breath with exertion in 20% on day 8, vs 30% in overall cohort). Rates of persistent symptoms at 30 days were lower in the mild initial symptom severity cohort, with no more than 1% reporting persistence of each individual symptom.

The heat map for moderate initial symptom severity had higher rates of all symptoms (compared to overall group and mild initial symptom severity). Differences were less for upper respiratory symptoms such as sinus congestion (peak prevalence 54% in moderate group compared with 45% overall) and greater for lower respiratory symptoms (e.g. shortness of breath with exertion 56% vs 30%), systemic symptoms (e.g. joint pain 36% vs 18%), and gastrointestinal symptoms (e.g. diarrhea 36% vs 21%). At 30 days the most frequent symptoms remaining were cough (9%), sinus congestion (8%), body aches (8%), joint pain (6%), loss of taste or smell (5%), shortness of breath with exertion (5%), and headache (4%). The heat map for the four nonhospitalized patients with severe initial symptom severity shows high prevalence

(100% within the first week) of chills, body aches, loss of smell or taste, sore throat, cough, chest tightness, and shortness of breath with exertion. At 30 days, 3 patients (75%) still had cough and shortness of breath with exertion.

**Timing of symptom onset of by system**

The median day of symptom onset determined by Kaplan-Meier curves is shown in figure 2. The onset for systemic and upper respiratory symptoms frequently occurred on day 1, with gastrointestinal and lower respiratory symptoms occurring later. Recognizing that cough can be a manifestation of upper airway or lower airway infections, we analyzed cough separately, finding a median start of 1 day (95% confidence interval 1 to 1). This was not different from the median start day for upper respiratory symptoms ($p=0.253$), but it was significantly different than the median start day for lower respiratory symptoms ($p<0.001$) so we grouped cough with the upper respiratory system.

**Duration of each symptom**

Figure 3 describes the median days and 95% confidence interval for each symptom obtained from Kaplan-Meier survival curves of the full study population (n=340), censoring hospitalized patients at time of admission (unless re-enrolled in VOMC after discharge). When present, cough had the longest duration with 17 days (95% confidence interval 15 to 21), followed by loss of smell or taste with 14 days (12 to 17) and sinus congestion with 13 days (11 to 15). Shortness of breath with exertion, when present, lasted 12 days (10 to 16).

Patients reporting improving symptoms could be discharged from VOMC with symptoms present. The percentage of patients reporting resolution of each symptom is presented in table 2. The symptoms most frequently unresolved at the time of the final phone call were cough (116 of 279 patients with cough, 42%), loss of smell or taste (89 of 233, 38%), sinus congestion (90 of 246, 37%), and shortness of breath with exertion (66 of 191, 35%).

**Table 2 Symptoms unresolved at last phone call**

| Symptom | Total patients with symptom | Number symptomatic at last phone call | Percent unresolved at last phone call |
|---|---|---|---|
| Fever | 145 | 18 | 12% |
| Chills | 196 | 20 | 10% |
| Body aches | 234 | 53 | 23% |
| Dizzy | 151 | 25 | 17% |
| Confusion | 20 | 3 | 15% |
| Headache | 259 | 56 | 22% |
| Loss of smell or taste | 233 | 89 | 38% |
| Congestion | 246 | 90 | 37% |
| Sore throat | 141 | 29 | 21% |
| Cough | 279 | 116 | 42% |
| Chest tightness | 150 | 27 | 18% |
| SOB at rest | 89 | 19 | 21% |
| SOB with exertion | 191 | 66 | 35% |
| Wheezing | 72 | 12 | 17% |
| Abdominal pain | 101 | 11 | 11% |
| Nausea | 126 | 24 | 19% |
| Diarrhea | 169 | 24 | 14% |
| Joint pain | 138 | 31 | 22% |
| Rash | 33 | 7 | 21% |



## Symptom duration predicted by covariates

Table 3 presents the results of the final AFT models with log-logistic distribution fitted individually for each symptom. The AFT deceleration factor is the factor by which the

survival time is multiplied for that group compared to the baseline group. For example, obesity was the only significant predictor of joint pain duration with 1.73 (95% CI 1.09-2.75) fold longer duration, which is 73% (95% CI 9-175%) longer symptoms. Asthma was the only significant predictor for wheezing, increasing duration by 160% (95% CI 37-394%). Asthma and black race were both predictors of duration for SOB at rest, with asthma increasing SOB duration by 101% (95% CI 22-232%) and black race by 178% (57-492%). Diarrhea is more complex. Patients with moderate initial symptom severity had 71% longer (95% CI 24-137%) duration of diarrhea, while blacks had a 44% (95% CI -16 to -63%) shorter duration of diarrhea. Initial symptom severity was a significant predictor for over half of our symptoms: body aches, chest tightness, chills, congestion, cough, diarrhea, dizziness, fever, headache, nausea, SOB with exertion, and sore throat. Moderate initial symptom severity increased average symptom duration by 63%. Severe initial symptom severity increased average symptom duration by 228% compared to those with mild initial symptom severity (see table 3 for details and confidence intervals). The residual plots to analyze goodness of fit for each symptom's model are in supplement figure 2.

**Table 3 Accelerated Failure Time model for each symptom modeled separately**

| Symptom | Covariate | Deceleration factor (95% CI) | p value |
|---|---|---|---|
| Abdominal Pain | Immune suppression | 7.50 (3.27-17.19) | <0.001 |
| Body Aches | Moderate initial symptom severity | 1.87 (1.44-2.42) | <0.001 |
| Body Aches | Severe initial symptom severity | 4.01 (1.66-9.67) | 0.002 |
| Chest Tightness | Moderate initial symptom severity | 1.33 (0.93-1.89) | 0.116 |
| Chest Tightness | Severe initial symptom severity | 4.27 (1.67-10.95) | 0.002 |
| Chills | Moderate initial symptom severity | 1.57 (1.21-2.03) | 0.001 |
| Chills | Severe initial symptom severity | 2.75 (1.28-5.90) | 0.010 |
| Confusion | Race = Black | 1.63 (0.96-2.77) | 0.070 |

| | | | |
|---|---|---|---|
| Confusion | Race = Other | 7.44 (3.98-13.92) | <0.001 |
| Sinus Congestion | Female | 1.55 (1.10-2.18) | 0.011 |
| Sinus Congestion | Moderate initial symptom severity | 1.62 (1.16-2.26) | 0.004 |
| Sinus Congestion | Severe initial symptom severity | 1.99 (0.59-6.71) | 0.270 |
| Cough | Moderate initial symptom severity | 1.54 (1.17-2.01) | 0.002 |
| Cough | Severe initial symptom severity | 3.49 (1.27-9.61) | 0.016 |
| Diarrhea | Moderate initial symptom severity | 1.71 (1.24-2.37) | 0.001 |
| Diarrhea | Severe initial symptom severity | 3.40 (0.91-12.69) | 0.068 |
| Diarrhea | Race = Black | 0.56 (0.37-0.84) | 0.005 |
| Diarrhea | Race = Other | 0.61 (0.39-0.96) | 0.033 |
| Dizziness | Moderate initial symptom severity | 1.78 (1.23-2.58) | 0.002 |
| Dizziness | Severe initial symptom severity | 6.07 (1.80-20.45) | 0.004 |
| Fever | Moderate initial symptom severity | 1.39(0.98-1.98) | 0.066 |
| Fever | Severe initial symptom severity | 4.84(1.55-15.06) | 0.007 |
| Headache | Moderate initial symptom severity | 2.15 (1.62-2.85) | <0.001 |
| Headache | Severe initial symptom severity | 2.15 (0.83-5.59) | 0.117 |
| Joint Pain | Obesity | 1.73 (1.09-2.75) | 0.02 |
| Loss of Smell or Taste | Female | 1.63 (1.25-2.14) | <0.001 |
| Loss of Smell or Taste | Immune suppression | 3.05 (1.48-6.30) | 0.003 |
| Nausea | Moderate initial symptom severity | 1.76 (1.17-2.65) | 0.007 |
| Nausea | Severe initial symptom severity | 2.75 (0.73-10.36) | 0.136 |
| SOB at rest | Asthma | 2.01 (1.22-3.32) | 0.006 |
| SOB at rest | Race = Black | 2.78 (1.57-4.92) | <0.001 |
| SOB at rest | Race = Other | 1.50 (0.78-2.87) | 0.223 |
| SOB with exertion | Moderate initial symptom severity | 1.75 (1.19-2.56) | 0.004 |
| SOB with exertion | Severe initial symptom severity | 1099097.56 (out of range) | 0.995 |
| Sore Throat | Moderate initial symptom severity | 1.25 (0.83-1.87) | 0.281 |
| Sore Throat | Severe initial symptom severity | 4.21 (1.70-10.45) | 0.002 |
| Wheezing | Asthma | 2.60 (1.37-4.94) | 0.003 |



## DISCUSSION

### Principal findings

Whereas other studies have looked at cross sectional analysis of covid-19 symptoms, our study describes the longitudinal symptom course over the acute illness period for a

telemedicine cohort, including the duration of reporting for each symptom and predictors of symptom duration.

We found that symptom onset starts with upper respiratory and systemic symptoms followed by lower respiratory and GI symptoms. This is consistent with the fact that infected individuals produce large quantities of virus in the upper respiratory tract during the prodromal period.[21] An important observation in this study is that initial symptom severity (at intake visit after test result) was a predictor for the symptom profile over time. Initial symptom severity predicts duration for the majority of symptoms, with significant associations for upper and lower respiratory symptoms as well as non-respiratory symptoms (including body aches, dizziness, chills, fever, headache, nausea and diarrhea). Notable exceptions were joint pain and wheezing whose only predictors of symptom duration were the underlying risk factors of obesity and asthma, respectively. While these associations make sense clinically, an explanation for immunosuppression leading to longer duration of specific symptoms (abdominal pain and loss of smell or taste) is less intuitive. To decrease the chance of finding false positives, we fit models only for covariates that were significant predictors of overall symptom duration with symptoms analyzed as strata, but some of the findings in the final models may be spurious. Nonetheless, the majority are very significant ($p<0.01$) along with clinically significant changes in duration.

**Comparison with other studies**

Initial symptoms reported are similar to previous studies of mild covid-19 and non-hospitalized subsets.[12,15] It differs from the overall reported literature, summarized in a systematic review of 148 studies.[14] Notably, fever was less common (n=121, 36%) compared with 78% in the systematic review, while other symptoms are more common, for example: headache (65% vs 13%), body aches (64% vs 17%), hyposmia (55% vs 25%). The higher frequency of multiple symptoms may be due to our systematic approach to symptom inquiry. Rate of fever may be underreported due to template wording “current fever” but also may be less frequent in this cohort as increased testing availability has expanded the symptom profile of “mild covid-19” patients eligible for screening (Box 1).

We find that the course of illness and predictors of symptom duration have not been well described and this is an important contribution of this analysis. Narrative reviews have noted symptom progression similar to our report[22] and the visual course reported here in heat map form illustrates the development of respiratory symptoms during and after the first week of illness among patients never requiring hospitalization for covid-19.

The persistence of symptoms identified in our study is also an important finding for clinical practice. In our experience providing in-person care, many patients present for evaluation of non-resolving symptoms during subacute or convalescent illness.[23] Other reports have noted long duration of medical leave among persons with covid-19,

for example first responders in New York (leave duration mean 25.3 days, SD=13.2).[24] We are able to differentiate the likelihood of prolonged symptoms in patients using mild and moderate initial symptom severity, which may aid in clinical counseling and anticipation of symptom recovery times. Given reports of delayed recovery of symptoms after hospitalization,[25] and in outpatients [18] the differentiation by symptom severity in outpatients is plausible.

Comparisons to reports of the severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) are limited as mild cases of these diseases were uncommon and most patients with SARS and MERS required hospital admission (requiring intensive care in >20% of SARS cases and >50% of MERS cases).[26, 27] The sequence of symptoms we describe for covid-19 is similar to descriptions of SARS, with initial presentation of systemic symptoms and cough, followed by lower respiratory symptoms and gastrointestinal manifestations.[26] Notable differences include that fever is universal in reports of SARS (99.9%) and upper respiratory symptoms are less common than with covid-19 (e.g. rhinorrhea, sore throat both <20%). Patients with MERS also more frequently have fever and dyspnea, with lower rates of upper respiratory symptoms.[27] Gastrointestinal symptoms appear at similar rates (20-30%) in SARS and MERS, despite the overall higher severity of respiratory disease.

**Strengths and limitations of study**

Our data on the course of symptoms in outpatients is robust due to the structure of the VOMC, which was staffed to meet the anticipated "surge" of patients in March-May 2020 and therefore had skilled providers contacting patients and completing full note templates regularly through the course of acute illness. Exclusion criteria was minimal and primarily in place to improve accuracy of symptom recollection. Missing clinical data were minimal (e.g. low risk patients contacted every 48 hours instead of 24 hours), allowing for standard approach to imputation.

The primary limitation of this study is that it represents a single-center cohort of patients screened during the early SARS-CoV-2 pandemic. Screening criteria favored the inclusion of working-age individuals in the cohort. We have limited numbers of patients with comorbidities and cannot therefore draw conclusions about the duration of symptoms related to specific conditions (e.g. chronic obstructive pulmonary disease). Because of the relatively small size of the cohort, we also have small numbers of less common symptoms (e.g. confusion and rash).

Another limitation of the structured VOMC cohort data is the time to intake visit. Usual care requires a positive SARS-CoV-2 test prior to enrollment, and delays in testing could attenuate recall of initial symptoms. We therefore limited the study to patients within 10 days of symptom onset and used chart review to verify symptoms reported in the screening process. Discharge timing in the VOMC was a limitation for our follow-up data: the VOMC discharge criteria mirrored the CDC terminology of symptom

"improvement," but not resolution. The percent of patients still symptomatic at the last phone call varied among symptoms (table 2). We find in other work (unpublished data) that minor residual symptoms are common after VOMC discharge (reported in 55 of 158, 34.8%, of patients contacted a mean of 37.9 days after discharge) and that few (n=7, 4.4%) have symptoms requiring medical follow-up (e.g. by a primary care physician or specialist).[28] These residual symptoms are not captured in the heat map data after their final VOMC call.

"Long covid" has now been described as symptoms persisting beyond the acute illness [29], including fatigue, palpitations, "brain fog" and other symptoms that were not known in March 2020. We have identified these symptoms in individual cases within the VOMC cohort who received prolonged care [18] but did not capture these specific symptoms during the acute care described in this study.

## CONCLUSION

Overall, we find that the symptom course of outpatients with covid-19 follows a pattern described in early observations with a typical illness course progressing from early symptoms (systemic, upper respiratory, and cough) to lower respiratory and gastrointestinal symptoms. We confirm that symptoms of altered smell or taste and headache are common in outpatients. Prolonged symptoms are common and the severity of symptoms in the acute phase of illness is the most significant predictor of disease duration.

## MANUSCRIPT INFORMATION

### Ethics

The study was approved by the Emory University Institutional Review Board (STUDY00000766), which granted both a waiver of informed consent and a waiver of the Health Information Portability and Privacy Act as the study posed no more than minimal risk.

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**Data Sharing Statement**: Deidentified data are available for sharing upon reasonable request to David Tong (ORCID 0000-0001-9761-6124). Data include patient demographics and comorbidities as well as symptom dates for all participants.

**Dissemination declaration**: We plan to disseminate our results publicly but it would not be feasible to reach discharged patients with study results and therefore we do not plan to contact study participants for dissemination.

**Conflict of Interest Disclosures**: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. Dr. G. O'Keefe served on an advisory board of Eyepoint Pharmaceuticals in 2019. It is unrelated to the current work.

**Author Contributions**:

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. David Tong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Transparency statement*: David Tong attests that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

*Concept and design:* JO, GO, DT

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## FIGURES

**Figure 1: Heatmap of incidence of individual symptoms by illness day**
Figure 1a: All patients, n=305 (% patients having symptom each day of covid-19 disease)
Figure 1b: Mild provider assessed symptom severity n=210
Figure 1c: Moderate provider assessed symptom severity n=91
Figure 1d: Severe provider assessed symptom severity n=4

**Figure 2: Median day of symptoms onset by system determined from Kaplan-Meier curves**

**Figure 3: Median duration of symptoms from Kaplan-Meier curves**

| Legend (Percent of patients experiencing a symptom each day of COVID disease) | 0 | 20 | 40 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|

All patients n=305

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| current fever | 22 | 22 | 21 | 20 | 18 | 18 | 16 | 14 | 11 | 8 | 10 | 9 | 5 | 3 | 2 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| chills | 27 | 34 | 35 | 34 | 31 | 29 | 26 | 19 | 18 | 12 | 10 | 9 | 6 | 5 | 5 | 4 | 3 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| body aches | 37 | 43 | 44 | 45 | 42 | 37 | 35 | 34 | 32 | 26 | 23 | 21 | 19 | 16 | 14 | 11 | 9 | 7 | 8 | 7 | 7 | 7 | 6 | 7 | 6 | 6 | 5 | 4 | 4 | 4 |
| dizziness when standing | 5 | 11 | 12 | 15 | 15 | 16 | 14 | 15 | 15 | 14 | 13 | 11 | 10 | 10 | 7 | 5 | 6 | 5 | 3 | 3 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 0 | 1 | 0 |
| confusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| headache | 37 | 44 | 45 | 43 | 42 | 38 | 35 | 33 | 29 | 27 | 25 | 23 | 20 | 19 | 17 | 14 | 12 | 11 | 10 | 10 | 8 | 8 | 9 | 8 | 5 | 7 | 6 | 4 | 4 | 2 |
| loss of smell or taste | 21 | 30 | 37 | 42 | 48 | 50 | 50 | 49 | 48 | 42 | 40 | 33 | 29 | 27 | 25 | 18 | 20 | 16 | 13 | 12 | 10 | 9 | 8 | 8 | 7 | 7 | 5 | 4 | 3 | 2 |
| sinus congestion | 32 | 37 | 42 | 45 | 45 | 43 | 44 | 41 | 40 | 38 | 37 | 32 | 29 | 25 | 24 | 20 | 21 | 19 | 16 | 12 | 12 | 11 | 8 | 8 | 7 | 6 | 5 | 4 | 4 | 3 |
| sore throat | 20 | 24 | 22 | 22 | 20 | 17 | 16 | 14 | 13 | 10 | 10 | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 3 | 3 | 3 | 2 | 3 | 3 | 2 | 1 | 2 | 1 | 1 |
| cough | 46 | 53 | 56 | 58 | 60 | 57 | 56 | 56 | 56 | 52 | 47 | 41 | 39 | 36 | 34 | 30 | 30 | 25 | 21 | 20 | 18 | 18 | 14 | 14 | 12 | 10 | 8 | 7 | 7 | 5 |
| chest tightness | 11 | 15 | 18 | 20 | 22 | 22 | 25 | 23 | 21 | 20 | 19 | 18 | 14 | 12 | 10 | 10 | 9 | 7 | 5 | 4 | 5 | 4 | 4 | 3 | 3 | 4 | 3 | 2 | 3 | 2 |
| shortness of breath at rest | 4 | 4 | 5 | 7 | 7 | 7 | 7 | 7 | 7 | 5 | 5 | 5 | 3 | 3 | 3 | 2 | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| shortness of breath with exertion | 13 | 17 | 20 | 21 | 23 | 26 | 29 | 30 | 30 | 27 | 25 | 24 | 22 | 21 | 20 | 20 | 16 | 14 | 13 | 13 | 11 | 10 | 9 | 8 | 7 | 8 | 8 | 5 | 6 | 3 |
| wheezing | 3 | 4 | 5 | 6 | 6 | 7 | 7 | 6 | 7 | 6 | 5 | 4 | 2 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 |
| abdominal pain | 3 | 4 | 6 | 7 | 10 | 10 | 7 | 7 | 7 | 7 | 5 | 3 | 2 | 3 | 3 | 2 | 2 | 1 | 1 | 0 | 2 | 1 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| nausea | 6 | 7 | 8 | 10 | 12 | 13 | 13 | 13 | 14 | 12 | 11 | 9 | 7 | 8 | 7 | 6 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 0 | 0 |
| diarrhea | 12 | 15 | 15 | 18 | 20 | 21 | 20 | 19 | 16 | 15 | 13 | 12 | 9 | 10 | 10 | 7 | 6 | 5 | 4 | 4 | 4 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |
| joint pain | 9 | 13 | 15 | 17 | 18 | 18 | 17 | 14 | 14 | 12 | 13 | 14 | 12 | 11 | 10 | 8 | 7 | 7 | 6 | 5 | 4 | 5 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 2 |
| rash | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 |

Mild initial symptoms = 210

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| current fever | 19 | 19 | 17 | 17 | 14 | 14 | 11 | 11 | 8 | 6 | 7 | 5 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| chills | 26 | 30 | 29 | 27 | 21 | 20 | 16 | 12 | 10 | 6 | 5 | 4 | 3 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| body aches | 34 | 38 | 38 | 36 | 30 | 26 | 23 | 22 | 20 | 18 | 16 | 13 | 13 | 9 | 7 | 6 | 4 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 2 | 2 | 2 | 1 | 1 | 1 |
| dizziness when standing | 2 | 7 | 8 | 10 | 10 | 10 | 6 | 7 | 8 | 9 | 8 | 6 | 6 | 5 | 4 | 2 | 2 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| confusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| headache | 34 | 40 | 40 | 37 | 35 | 31 | 29 | 25 | 20 | 20 | 20 | 14 | 12 | 13 | 10 | 10 | 7 | 6 | 7 | 6 | 5 | 5 | 6 | 4 | 3 | 4 | 4 | 2 | 2 | 1 |
| loss of smell or taste | 21 | 27 | 34 | 38 | 44 | 46 | 45 | 43 | 42 | 38 | 36 | 27 | 24 | 23 | 21 | 14 | 15 | 10 | 9 | 8 | 7 | 6 | 5 | 5 | 4 | 5 | 3 | 1 | 1 | 0 |
| sinus congestion | 31 | 36 | 42 | 45 | 44 | 42 | 40 | 37 | 34 | 32 | 33 | 25 | 24 | 20 | 18 | 17 | 14 | 13 | 9 | 7 | 6 | 6 | 5 | 4 | 4 | 2 | 2 | 1 | 1 | 1 |
| sore throat | 19 | 24 | 22 | 21 | 19 | 15 | 12 | 11 | 10 | 9 | 10 | 6 | 5 | 4 | 4 | 4 | 5 | 5 | 6 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| cough | 40 | 47 | 48 | 50 | 52 | 50 | 47 | 46 | 47 | 43 | 38 | 31 | 29 | 27 | 24 | 21 | 20 | 18 | 13 | 11 | 11 | 11 | 9 | 7 | 6 | 5 | 4 | 1 | 3 | 1 |
| chest tightness | 9 | 10 | 12 | 14 | 17 | 17 | 16 | 15 | 14 | 13 | 14 | 13 | 10 | 7 | 7 | 7 | 6 | 6 | 4 | 3 | 3 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| shortness of breath at rest | 3 | 3 | 2 | 3 | 3 | 4 | 3 | 5 | 4 | 3 | 3 | 4 | 2 | 3 | 2 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| shortness of breath with exertion | 6 | 8 | 10 | 11 | 13 | 15 | 17 | 20 | 18 | 16 | 15 | 14 | 13 | 13 | 10 | 13 | 9 | 8 | 8 | 7 | 6 | 5 | 5 | 4 | 3 | 3 | 3 | 1 | 2 | 1 |
| wheezing | 2 | 2 | 2 | 3 | 4 | 5 | 4 | 3 | 4 | 4 | 4 | 4 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| abdominal pain | 3 | 1 | 3 | 5 | 7 | 7 | 4 | 5 | 4 | 5 | 3 | 2 | 1 | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nausea | 3 | 4 | 5 | 8 | 9 | 10 | 9 | 9 | 11 | 9 | 9 | 5 | 3 | 5 | 5 | 3 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| diarrhea | 10 | 10 | 10 | 13 | 14 | 15 | 13 | 14 | 10 | 10 | 8 | 7 | 6 | 8 | 7 | 3 | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| joint pain | 7 | 9 | 10 | 11 | 12 | 11 | 8 | 7 | 6 | 6 | 6 | 8 | 7 | 7 | 6 | 5 | 3 | 3 | 2 | 3 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 0 |
| rash | 0 | 1 | 0 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |

Moderate initial symptoms n = 91

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| current fever | 27 | 29 | 28 | 25 | 25 | 26 | 26 | 17 | 15 | 10 | 15 | 16 | 8 | 6 | 4 | 3 | 2 | 3 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 0 | 2 | 1 | 2 | 1 |
| chills | 28 | 41 | 46 | 48 | 49 | 48 | 49 | 31 | 34 | 24 | 19 | 16 | 12 | 7 | 7 | 7 | 5 | 2 | 2 | 2 | 3 | 2 | 5 | 5 | 3 | 3 | 3 | 4 | 5 | 1 |
| body aches | 41 | 53 | 59 | 67 | 67 | 59 | 61 | 58 | 58 | 41 | 37 | 36 | 28 | 28 | 27 | 20 | 19 | 13 | 16 | 14 | 16 | 13 | 12 | 12 | 14 | 13 | 10 | 9 | 9 | 8 |
| dizziness when standing | 12 | 19 | 21 | 25 | 26 | 27 | 30 | 31 | 31 | 26 | 25 | 24 | 19 | 18 | 13 | 9 | 14 | 10 | 8 | 8 | 5 | 3 | 5 | 3 | 5 | 2 | 1 | 1 | 1 | 1 |
| confusion | 1 | 1 | 0 | 0 | 0 | 0 | 3 | 2 | 1 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| headache | 43 | 50 | 56 | 58 | 56 | 52 | 50 | 50 | 49 | 42 | 37 | 42 | 35 | 31 | 32 | 23 | 23 | 21 | 17 | 19 | 16 | 15 | 14 | 16 | 8 | 13 | 9 | 9 | 8 | 4 |
| loss of smell or taste | 21 | 36 | 41 | 50 | 54 | 57 | 60 | 62 | 59 | 50 | 50 | 45 | 39 | 32 | 30 | 25 | 26 | 26 | 18 | 19 | 16 | 16 | 14 | 14 | 10 | 12 | 9 | 9 | 6 | 5 |
| sinus congestion | 35 | 41 | 43 | 45 | 49 | 46 | 54 | 51 | 53 | 50 | 45 | 47 | 39 | 36 | 39 | 29 | 36 | 31 | 30 | 24 | 26 | 23 | 15 | 18 | 13 | 16 | 13 | 10 | 10 | 8 |
| sore throat | 23 | 24 | 23 | 21 | 19 | 19 | 20 | 17 | 18 | 10 | 9 | 8 | 8 | 14 | 13 | 9 | 6 | 7 | 5 | 3 | 4 | 6 | 4 | 9 | 7 | 7 | 4 | 5 | 3 | 2 |
| cough | 58 | 67 | 72 | 74 | 75 | 73 | 74 | 76 | 76 | 71 | 64 | 62 | 61 | 54 | 52 | 47 | 48 | 39 | 37 | 38 | 31 | 31 | 23 | 27 | 20 | 19 | 16 | 16 | 13 | 9 |
| chest tightness | 14 | 21 | 28 | 31 | 30 | 34 | 42 | 39 | 37 | 30 | 26 | 27 | 20 | 21 | 16 | 13 | 10 | 7 | 7 | 6 | 7 | 8 | 7 | 8 | 6 | 9 | 8 | 6 | 8 | 4 |
| shortness of breath at rest | 8 | 8 | 10 | 15 | 15 | 14 | 16 | 9 | 13 | 7 | 8 | 5 | 3 | 3 | 5 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 1 | 3 | 2 | 2 | 1 | 1 |
| shortness of breath with exertion | 27 | 35 | 39 | 42 | 43 | 49 | 53 | 50 | 56 | 50 | 45 | 45 | 39 | 38 | 39 | 31 | 29 | 25 | 21 | 24 | 19 | 18 | 15 | 15 | 12 | 17 | 14 | 12 | 9 | 5 |
| wheezing | 5 | 8 | 10 | 13 | 10 | 12 | 15 | 15 | 14 | 10 | 8 | 5 | 4 | 3 | 3 | 3 | 3 | 2 | 2 | 3 | 5 | 5 | 2 | 3 | 3 | 2 | 3 | 2 | 2 | 1 |
| abdominal pain | 4 | 9 | 13 | 12 | 17 | 15 | 13 | 12 | 14 | 12 | 10 | 6 | 4 | 6 | 7 | 6 | 5 | 4 | 5 | 1 | 5 | 5 | 6 | 5 | 2 | 4 | 2 | 2 | 0 | 3 |
| nausea | 13 | 13 | 15 | 14 | 17 | 19 | 24 | 23 | 21 | 19 | 17 | 17 | 14 | 14 | 12 | 12 | 7 | 7 | 6 | 6 | 7 | 6 | 7 | 7 | 4 | 5 | 4 | 3 | 2 | 2 |
| diarrhea | 17 | 25 | 28 | 28 | 31 | 36 | 35 | 31 | 31 | 26 | 25 | 24 | 18 | 15 | 18 | 16 | 14 | 15 | 12 | 10 | 9 | 6 | 6 | 5 | 5 | 3 | 4 | 3 | 1 | 0 |
| joint pain | 14 | 21 | 28 | 31 | 32 | 32 | 36 | 31 | 30 | 25 | 28 | 28 | 21 | 21 | 19 | 16 | 17 | 16 | 15 | 9 | 8 | 6 | 7 | 7 | 6 | 8 | 9 | 7 | 6 | 6 |
| rash | 3 | 3 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 2 | 3 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 1 |

Severe initial symptoms n = 4

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| current fever | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 0 |
| chills | 75 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 50 | 50 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| body aches | 75 | 75 | 75 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 75 | 75 | 25 | 25 | 50 | 50 | 75 | 50 | 50 | 50 | 50 | 50 | 50 |
| dizziness when standing | 25 | 25 | 25 | 25 | 25 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 50 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 0 |
| confusion | 0 | 0 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| headache | 50 | 75 | 75 | 75 | 75 | 75 | 50 | 50 | 50 | 50 | 50 | 50 | 75 | 75 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| loss of smell or taste | 50 | 50 | 50 | 75 | 75 | 100 | 100 | 75 | 75 | 100 | 75 | 75 | 100 | 100 | 100 | 75 | 100 | 50 | 75 | 50 | 25 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 25 |
| sinus congestion | 25 | 25 | 25 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 25 | 25 | 50 | 50 | 50 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| sore throat | 50 | 50 | 50 | 50 | 100 | 50 | 75 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 50 | 50 |
| cough | 75 | 75 | 75 | 100 | 100 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 75 | 75 | 100 | 75 | 50 | 75 | 75 | 75 |
| chest tightness | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 100 | 75 | 75 | 75 | 75 | 75 | 75 | 75 | 100 | 100 | 75 | 50 | 25 | 25 | 25 | 50 | 25 | 75 | 50 | 50 | 50 | 50 | 50 |
| shortness of breath at rest | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 50 | 25 | 25 | 25 | 25 | 25 | 25 | 50 | 50 | 75 | 50 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| shortness of breath with exertion | 75 | 75 | 75 | 75 | 75 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 75 | 75 | 75 | 75 | 100 | 75 | 100 | 75 | 100 | 75 |
| wheezing | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 0 | 0 | 0 | 25 | 25 |
| abdominal pain | 0 | 0 | 0 | 0 | 0 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nausea | 25 | 25 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 |
| diarrhea | 0 | 0 | 0 | 0 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 0 | 0 | 25 | 0 | 0 | 25 | 25 |
| joint pain | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 50 | 25 | 25 | 25 | 25 | 0 | 0 | 0 | 0 | 0 | 25 | 25 | 50 | 50 | 25 | 0 | 0 | 0 | 0 | 0 | 0 |
| rash | 0 | 0 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 50 | 25 | 25 |

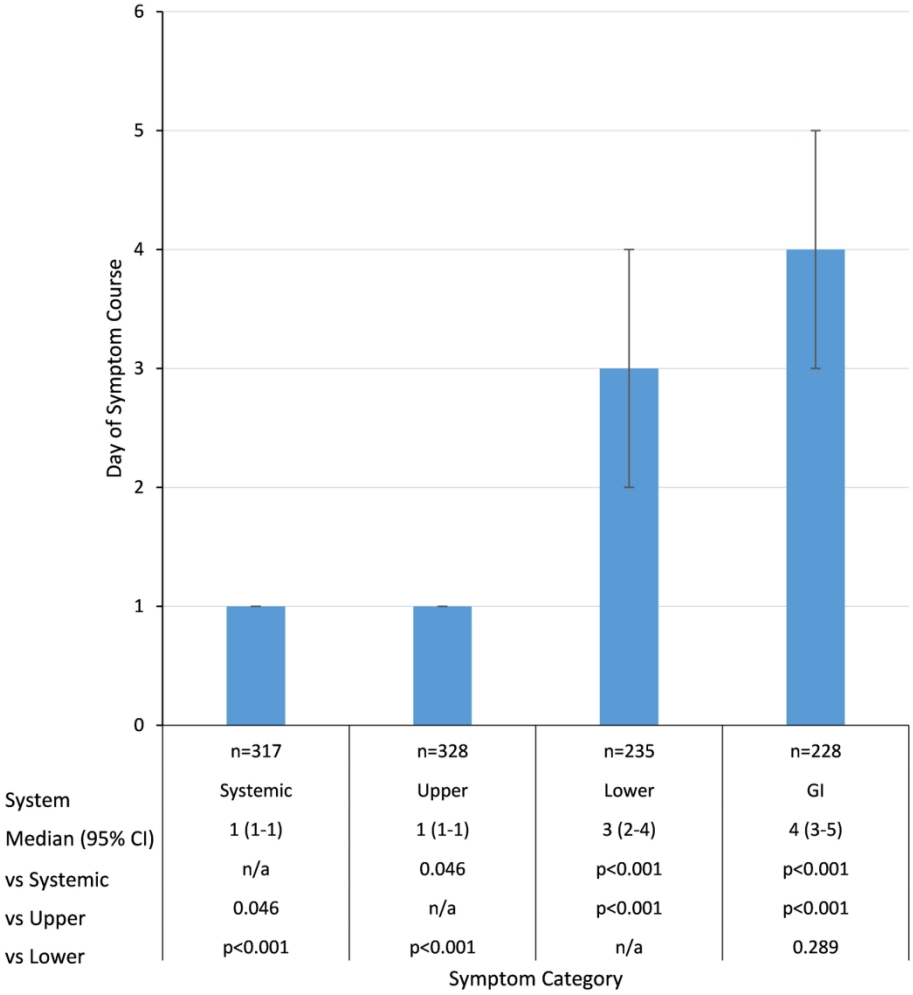



Figure 2: Median day of symptoms onset by system determined from Kaplan-Meier curves

149x188mm (300 x 300 DPI)

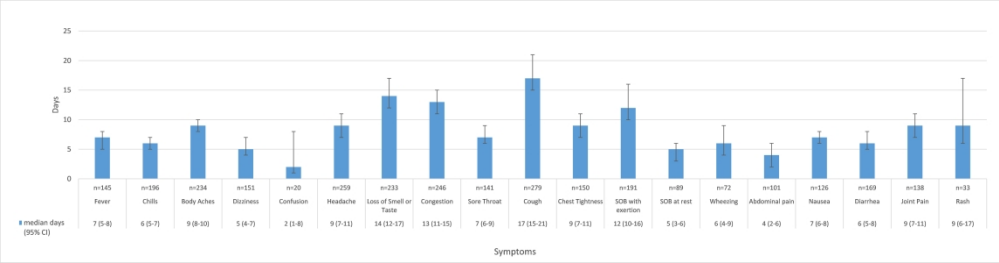



Figure 3: Median duration of symptoms from Kaplan-Meier curves

400x105mm (300 x 300 DPI)

Table 1 Cox models with AIC (time interaction terms for time varying covariates)

| Symptom | Covariate | Hazard Ratio (95% CI) | p value | AIC |
|---|---|---|---|---|
| Abdominal pain | Immune suppression | 0.03 (0.002-0.37) | 0.006 | 649.88 |
| | time*Immune suppression | 1.15 (1.02-1.31) | 0.024 | |
| Body Aches | Female | 1.30 (0.71-2.38) | 0.395 | 1657.02 |
| | Moderate initial symptom severity | 0.50 (0.36-0.68) | <0.001 | |
| | Severe initial symptom severity | 0.28 (0.09-0.90) | 0.003 | |
| | time*Female | 0.90 (0.84-0.96) | 0.001 | |
| Chest Tightness | Female | 0.7 (0.46-1.05) | 0.085 | 1003.77 |
| | Moderate initial symptom severity | 0.69 (0.47-1) | 0.050 | |
| | Severe initial symptom severity | 0.28 (0.09-0.91) | 0.033 | |
| Chills | Female | 0.72 (0.52-0.99) | 0.045 | 1523.19 |
| | Moderate initial symptom severity | 0.57 (0.42-0.78) | <0.001 | |
| | Severe initial symptom severity | 0.36 (0.15-0.91) | 0.031 | |
| Confusion | Obesity | 3.72 (1.21-11.47) | 0.022 | 68.68 |
| Cough | Moderate initial symptom severity | 0.67 (0.48-0.93) | 0.017 | 1548.72 |
| | Severe initial symptom severity | 0.24 (0.06-0.99) | 0.049 | |
| | Asthma | 0.66 (0.4-1.08) | 0.098 | |
| Fever | Moderate initial symptom severity | 0.73 (0.51-1.06) | 0.098 | 1005.47 |
| | Severe initial symptom severity | 0.17 (0.04-0.74) | 0.019 | |
| | Immune suppression | 0.45 (0.2-0.98) | 0.043 | |
| | Obesity | 0.63 (0.42-0.93) | 0.020 | |
| Diarrhea | Moderate initial symptom severity | 0.62 (0.44-0.87) | 0.006 | 1194.12 |
| | Severe initial symptom severity | 0.29 (0.07-1.21) | 0.090 | |
| | AgeGTE60 | 1.77 (1.14-2.75) | 0.011 | |
| Dizziness | Moderate initial symptom severity | 0.6 (0.42-0.86) | 0.006 | 1030.48 |
| | Severe initial symptom severity | 0.24 (0.06-1) | 0.050 | |
| HA | Female | 0.62 (0.46-0.84) | 0.002 | 1902.62 |
| | Moderate initial symptom severity | 0.5 (0.37-0.68) | <0.001 | |
| | Severe initial symptom severity | 0.49 (0.16-1.55) | 0.226 | |
| Joint Pain | Obesity | 0.67 (0.44-1.02) | 0.060 | 880.83 |
| Loss Smell or Taste | Female | 0.52 (0.36-0.74) | <0.001 | 1305.62 |
| | Immune suppression | 0.25 (0.08-0.78) | 0.017 | |
| Nausea | Female | 0.56 (0.35-0.9) | 0.016 | 802.69 |
| Rash | no significant covariates | | | |
| SOB at rest | no significant covariates | | | |
| SOB with exertion | no significant covariates | | | |
| Congestion | Female | 0.65 (0.47-0.91) | 0.013 | 1472.22 |
| | Moderate initial symptom severity | 0.6 (0.43-0.85) | 0.004 | |
| | Severe initial symptom severity | 0.64 (0.16-2.59) | 0.528 | |
| Sore Throat | Moderate initial symptom severity | 0.88 (0.49-1.59) | 0.682 | 891.69 |
| | Severe initial symptom severity | 0.04 (0-1.01) | 0.051 | |
| | time*Moderate initial symptom severity | 0.97 (0.92-1.02) | 0.250 | |
| | time*Severe initial symptom severity | 1.11 (0.97-1.27) | 0.145 | |
| Wheezing | Asthma | 0.37 (0.19-0.7) | 0.002 | 396.64 |

Table 2 Univariate analysis of covariates predicting all symptoms but analyzed as strata

| Covariate | log logistic p value | log normal p value |
|---|---|---|
| Female | <0.001 | <0.001 |
| Moderate initial symptom severity | <0.001 | <0.001 |
| Severe initial symptom severity | <0.001 | <0.001 |
| Race = Black | 0.634 | <0.001 |
| Race = Others | <0.001 | <0.001 |
| Age ≥ 60 | 0.122 | 0.101 |
| Alcohol abuse | 0.339 | 0.340 |
| Asthma | <0.001 | <0.001 |
| Cancer | 0.225 | 0.322 |
| Pregnant | 0.066 | 0.056 |
| COPD | 0.319 | 0.164 |
| CAD | 0.173 | 0.309 |
| Diabetes | 0.437 | 0.416 |
| Drug abuse | 0.373 | 0.359 |
| Heart failure | 0.303 | 0.245 |
| Hypertension | 0.100 | 0.241 |
| Immune suppression | <0.001 | <0.001 |
| Lung disease | 0.156 | 0.377 |
| Obesity | <0.001 | <0.001 |
| Renal disease | 0.961 | 0.932 |

Table 3 Aikake information criteria for different distributions in the accelerated failure time model before removing nonsignificant covariates

| | Log normal | Log logistic | Exponential* | Weibull | Logistic | Gaussian | Cox PH |
|---|---|---|---|---|---|---|---|
| Abdominal Pain | 513.24 | 520.12 | 534.11 | 534.11 | 630.11 | 652.56 | 649.88 |
| Body Aches | 1270.64 | 1267.81 | 1303.56 | 1297.08 | 1434.51 | 1460.96 | 1657.02 |
| Chest Tightness | 870.16 | 872.76 | 873.78 | 870.23 | 938.33 | 945.44 | 1003.77 |
| Chills | 1040.50 | 1044.37 | 1069.62 | 1049.86 | 1147.28 | 1191.61 | 1523.19 |
| Confusion | 52.71 | 53.72 | 65.02 | 55.88 | 80.99 | 84.83 | 68.68 |
| Cough | 1364.56 | 1357.13 | 1371.20 | 1353.51 | 1438.89 | 1434.31 | 1548.72 |
| Fever | 774.82 | 782.74 | 780.88 | 774.37 | 848.20 | 855.35 | 1005.47 |
| Diarrhea | 901.05 | 909.57 | 915.87 | 910.76 | 1004.42 | 1015.55 | 1194.12 |
| Dizziness | 773.75 | 781.33 | 792.40 | 790.78 | 894.19 | 910.16 | 1030.48 |
| HA | 1421.81 | 1425.91 | 1451.17 | 1439.46 | 1596.60 | 1615.10 | 1902.62 |
| Joint Pain | 763.35 | 766.31 | 770.20 | 772.18 | 867.79 | 875.86 | 880.83 |
| Loss of Smell Taste | 1129.68 | 1122.00 | 1148.41 | 1122.00 | 1183.54 | 1184.97 | 1305.62 |
| Nausea | 662.65 | 666.80 | 667.27 | 671.80 | 741.28 | 750.72 | 802.69 |
| Rash | 197.16 | 198.85 | 180.30 | 195.28 | 197.90 | 196.01 | no covariates |
| SOB at rest | 395.17 | 397.92 | 410.46 | 411.75 | 481.16 | 503.80 | no covariates |
| SOB with exertion | 966.97 | 969.14 | 969.58 | 969.61 | 1059.54 | 1062.07 | no covariates |
| Congestion | 1219.23 | 1217.56 | 1221.87 | 1217.33 | 1333.03 | 1337.98 | 1472.22 |
| Sore Throat | 753.64 | 757.36 | 763.23 | 761.29 | 850.99 | 869.91 | 891.69 |
| Wheezing | 372.37 | 375.22 | 373.32 | 374.98 | 436.12 | 445.80 | 396.64 |

*Exponential distribution can not be modeled with symptoms as strata so the variables that were significant for the loglogistic distribution when screened with symptom as strata were used for the exponential model to calculate the AFT exponential distribution model to obtain the AIC.

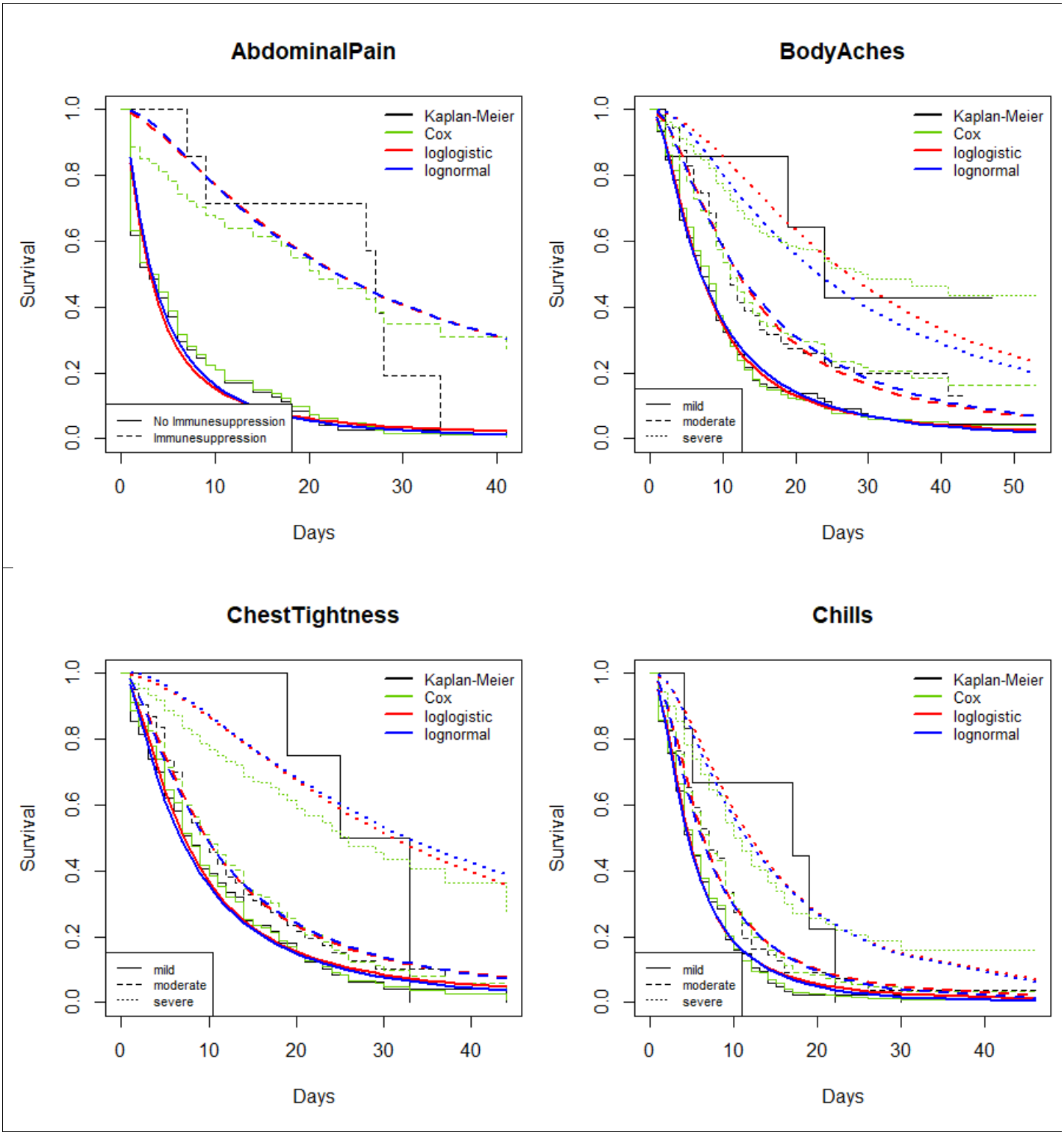
Table 4 Comparing final models for lognormal and loglogistic distributions

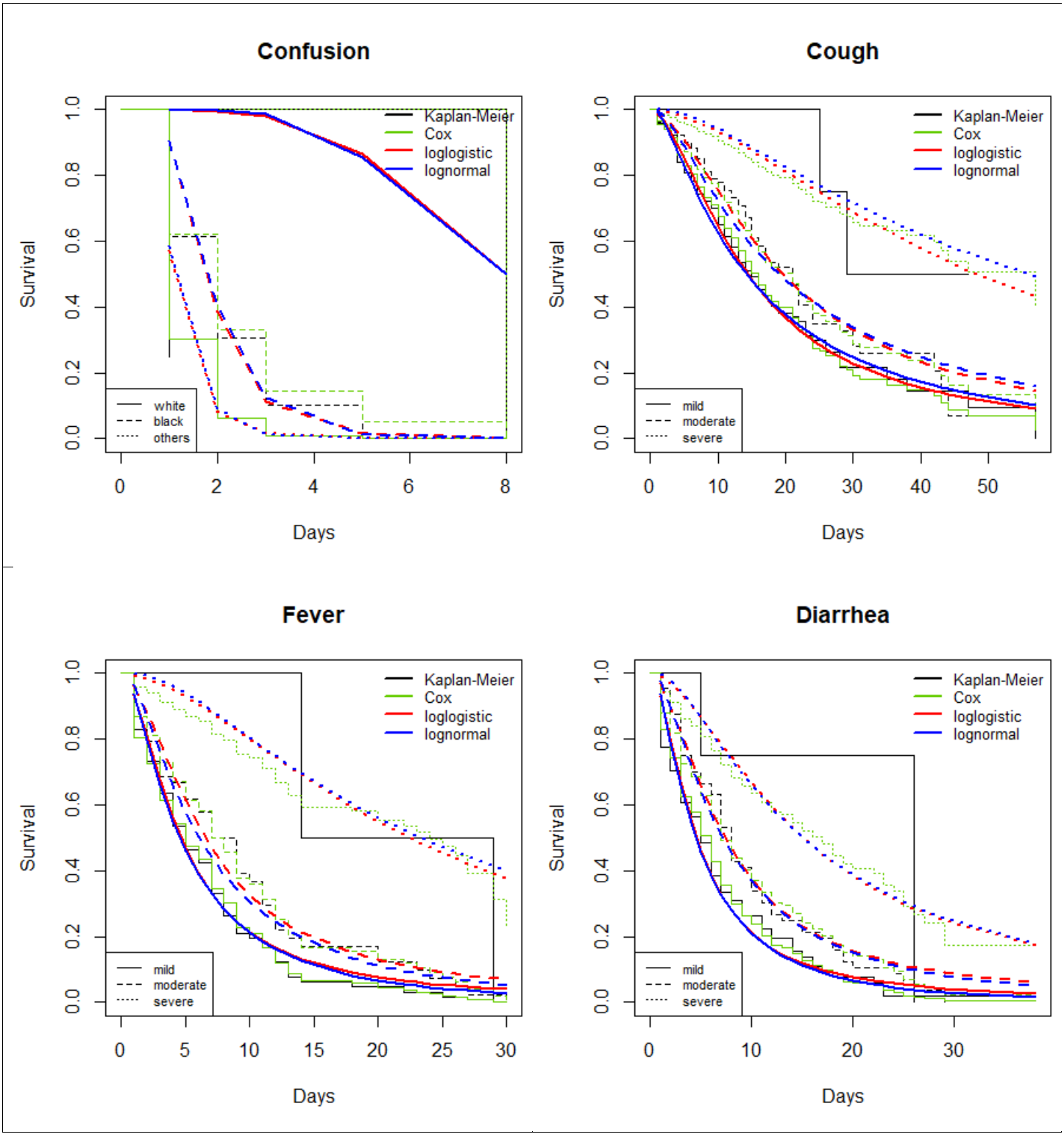
| Symptom | Predictor | Lognormal Deceleration factor (95% CI) | Lognormal p value | Loglogistic Deceleration factor (95% CI) | Loglogistic p value |
|---|---|---|---|---|---|
| Abdominal Pain | Immune suppression | 6.96 (2.92-16.57) | <0.001 | 7.50 (3.27-17.19) | <0.001 |
| Body Aches | Moderate initial symptom severity | 1.90 (1.44-2.49) | <0.001 | 1.87 (1.44-2.42) | <0.001 |
| Body Aches | Severe initial symptom severity | 3.39 (1.43-8.06) | 0.006 | 4.01 (1.66-9.67) | 0.002 |
| Chest Tightness | Moderate initial symptom severity | 1.41 (0.99-2.01) | 0.056 | 1.33 (0.93-1.89) | 0.116 |
| Chest Tightness | Severe initial symptom severity | 4.84 (1.63-14.37) | 0.004 | 4.27 (1.67-10.95) | 0.002 |
| Chills | Moderate initial symptom severity | 1.54 (1.19-2.00) | 0.001 | 1.57 (1.21-2.03) | 0.001 |
| Chills | Severe initial symptom severity | 2.71 (1.26-5.83) | 0.011 | 2.75 (1.28-5.90) | 0.010 |
| Confusion | Race = Black | 1.61 (0.90-2.88) | 0.106 | 1.63 (0.96-2.77) | 0.070 |
| Confusion | Race = Other | 7.25 (3.36-15.68) | <0.001 | 7.44 (3.98-13.92) | <0.001 |
| Congestion | Female | 1.54 (1.08-2.19) | 0.016 | 1.55 (1.10-2.18) | 0.011 |
| Congestion | Moderate initial symptom severity | 1.55 (1.10-2.19) | 0.012 | 1.62 (1.16-2.26) | 0.004 |
| Congestion | Severe initial symptom severity | 2.27 (0.54-9.53) | 0.265 | 1.99 (0.59-6.71) | 0.270 |
| Cough | Moderate initial symptom severity | 1.51 (1.12-2.02) | 0.006 | 1.54 (1.17-2.01) | 0.002 |
| Cough | Severe initial symptom severity | 4.09 (1.28-13.02) | 0.017 | 3.49 (1.27-9.61) | 0.016 |
| Diarrhea | Moderate initial symptom severity | 1.68 (1.23-2.30) | 0.001 | 1.71 (1.24-2.37) | 0.001 |
| Diarrhea | Severe initial symptom severity | 3.4 (1.00-11.63) | 0.051 | 3.40 (0.91-12.69) | 0.068 |
| Diarrhea | Race = Black | 0.57 (0.38-0.85) | 0.007 | 0.56 (0.37-0.84) | 0.005 |
| Diarrhea | Race = Other | 0.62 (0.40-0.97) | 0.037 | 0.61 (0.39-0.96) | 0.033 |
| Dizziness | Moderate initial symptom severity | 1.71 (1.21-2.43) | 0.003 | 1.78 (1.23-2.58) | 0.002 |
| Dizziness | Severe initial symptom severity | 6.06 (1.53-24.03) | 0.010 | 6.07 (1.80-20.45) | 0.004 |
| Fever | Moderate initial symptom severity | 1.20 (0.86-1.68) | 0.289 | 1.39(0.98-1.98) | 0.066 |
| Fever | Severe initial symptom severity | 4.43 (1.24-15.9) | 0.022 | 4.84(1.55-15.06) | 0.007 |
| Fever | Immune suppression | 2.04 (1.06-3.92) | 0.033 | not in model | |
| Fever | Obesity | 1.45 (1.01-2.07) | 0.043 | not in model | |
| Headache | Moderate initial symptom severity | 2.16 (1.62-2.88) | <0.001 | 2.15 (1.62-2.85) | <0.001 |
| Headache | Severe initial symptom severity | 2.42 (0.93-6.30) | 0.070 | 2.15 (0.83-5.59) | 0.117 |
| Joint Pain | Obesity | 1.63 (1.04-2.57) | 0.035 | 1.73 (1.09-2.75) | 0.020 |
| Loss of Smell or Taste | Female | 1.69 (1.26-2.26) | <0.001 | 1.63 (1.25-2.14) | <0.001 |
| Loss of Smell or Taste | Immune suppression | 3.41 (1.52-7.66) | 0.003 | 3.05 (1.48-6.30) | 0.003 |
| Nausea | Moderate initial symptom severity | 1.66 (1.12-2.47) | 0.012 | 1.76 (1.17-2.65) | 0.007 |
| Nausea | Severe initial symptom severity | 2.45 (0.73-8.24) | 0.148 | 2.75 (0.73-10.36) | 0.136 |
| SOB at rest | Asthma | 2.00 (1.21-3.30) | 0.007 | 2.01 (1.22-3.32) | 0.006 |
| SOB at rest | Race = Black | 2.62 (1.46-4.69) | 0.001 | 2.78 (1.57-4.92) | <0.001 |
| SOB at rest | Race = Other | 1.50 (0.78-2.88) | 0.219 | 1.50 (0.78-2.87) | 0.223 |
| SOB with exertion | Moderate initial symptom severity | 1.78 (1.21-2.62) | 0.003 | 1.75 (1.19-2.56) | 0.004 |
| SOB with exertion | Severe initial symptom severity | 3756.98 (out of range | 0.990 | 1099097.56 (out of range) | 0.995 |
| Sore Throat | Moderate initial symptom severity | 1.22 (0.83-1.79) | 0.321 | 1.25 (0.83-1.87) | 0.281 |
| Sore Throat | Severe initial symptom severity | 4.23 (1.45-12.32) | 0.008 | 4.21 (1.70-10.45) | 0.002 |
| Wheezing | Asthma | 2.24 (1.23-4.05) | 0.008 | 2.60 (1.37-4.94) | 0.003 |

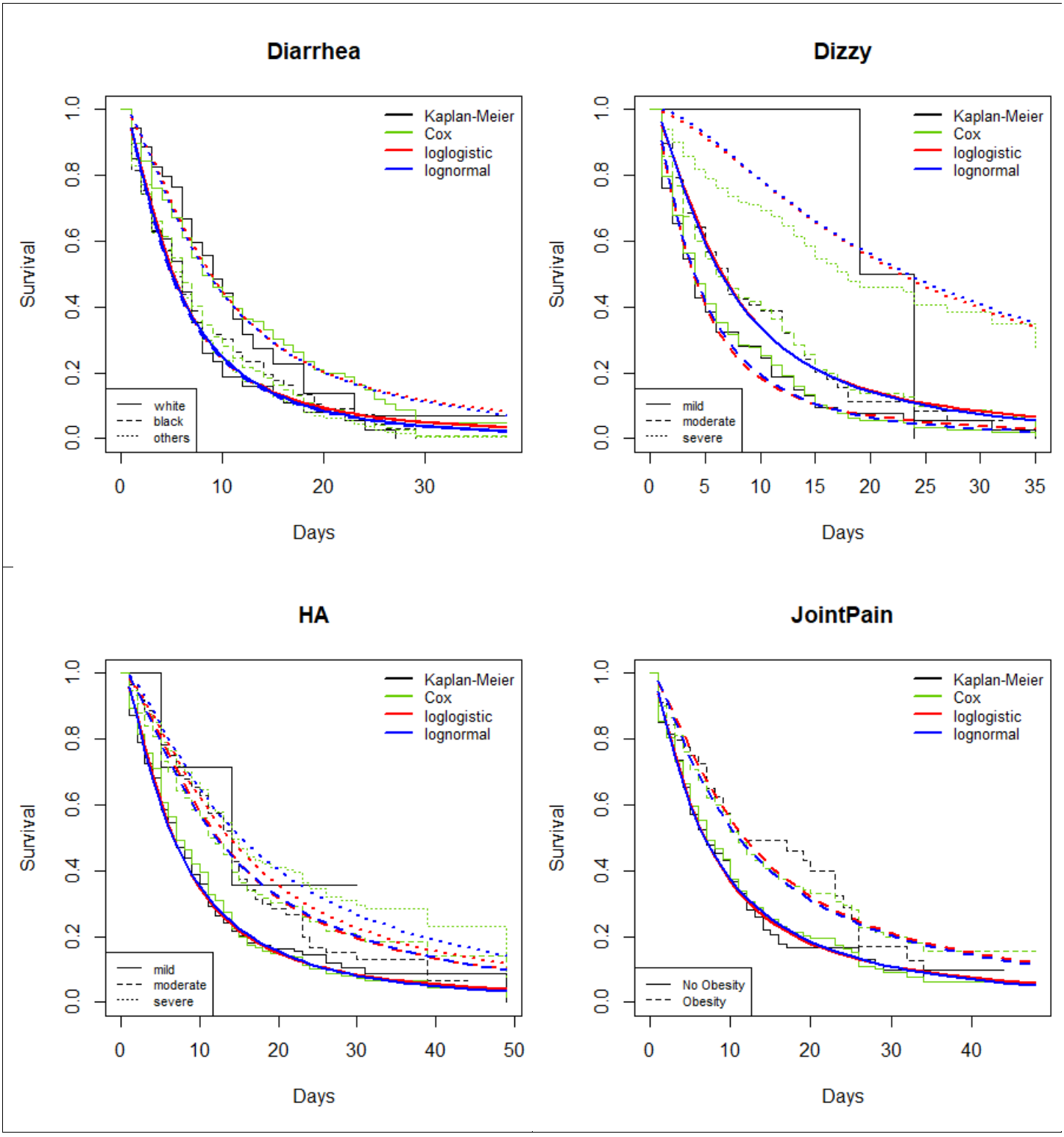
Table 5 AIC for AFT models for each symptoms similar comparing imputing provider assessed symptom severity with using related observation of self reported symptom severity

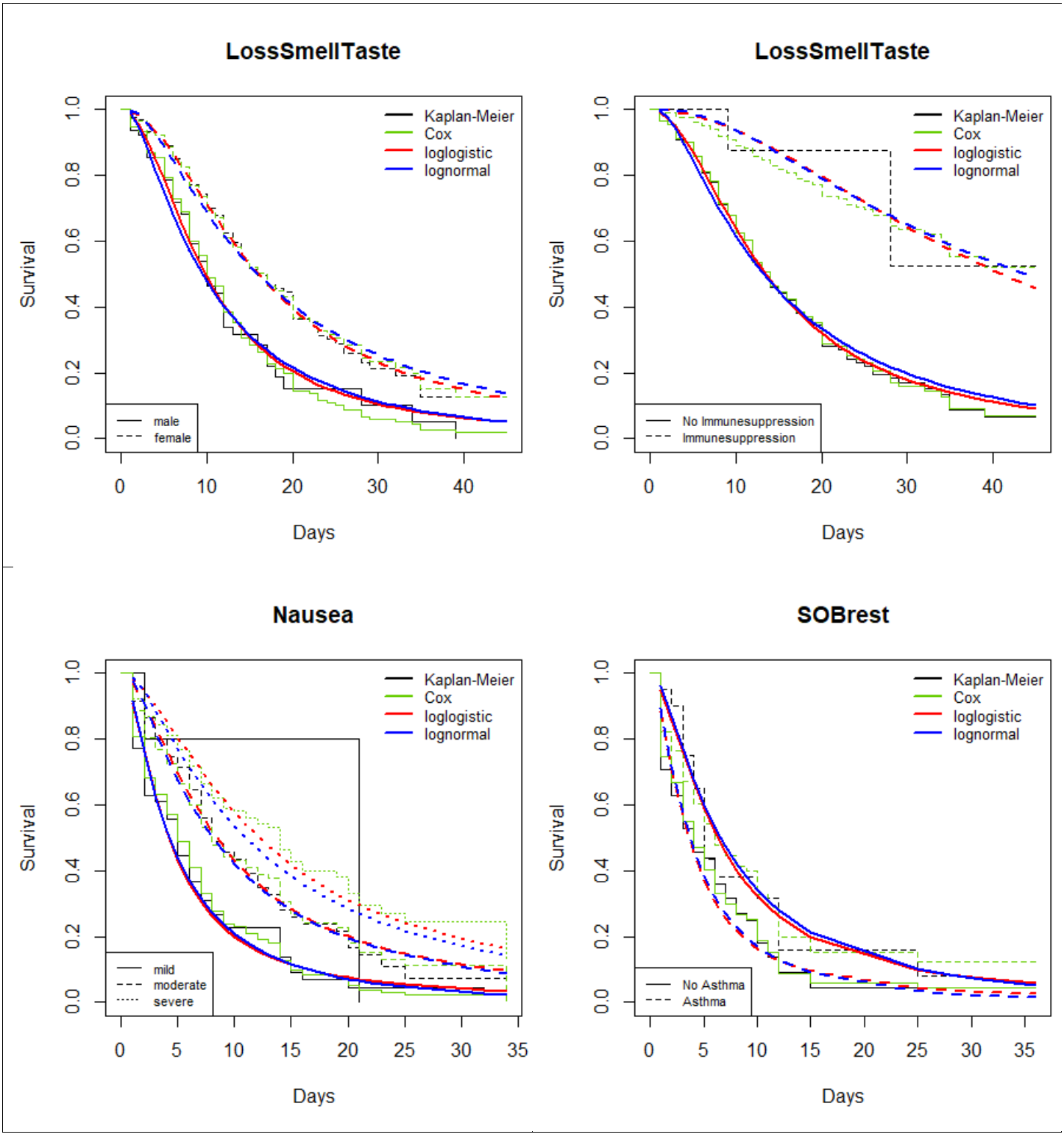
| | Using patient self reported symptom severity if provider assessed symptom severity not done (loglogistic distribution) | Imputed initial provider assessed symptom severity if missing Loglogistic distribution |
|---|---|---|
| Abdominal Pain | 520.1186 | 520.1186 |
| Body Aches | 1267.808 | 1273.045 |
| Chest Tightness | 872.7642 | 872.3861 |
| Chills | 1044.367 | 1049.595 |
| Confusion | 53.71975 | 53.71975 |
| Cough | 1357.125 | 1361.773 |
| Fever | 784.0569 | 783.9897 |
| Diarrhea | 909.5731 | 911.5716 |
| Dizzy | 781.3268 | 783.1709 |
| HA | 1425.913 | 1436.004 |
| Joint Pain | 766.3087 | 766.3087 |
| Loss of Smell or Taste | 1122.003 | 1122.003 |
| Nausea | 666.8013 | 662.8563 |
| Rash | 185.651 | 185.651 |
| SOB at rest | 397.9211 | 397.9211 |
| SOB with exertion | 969.144 | 972.3846 |
| Congestion | 1217.556 | 1219.118 |
| Sore Throat | 757.3605 | 757.5769 |
| Wheezing | 375.2166 | 375.2166 |

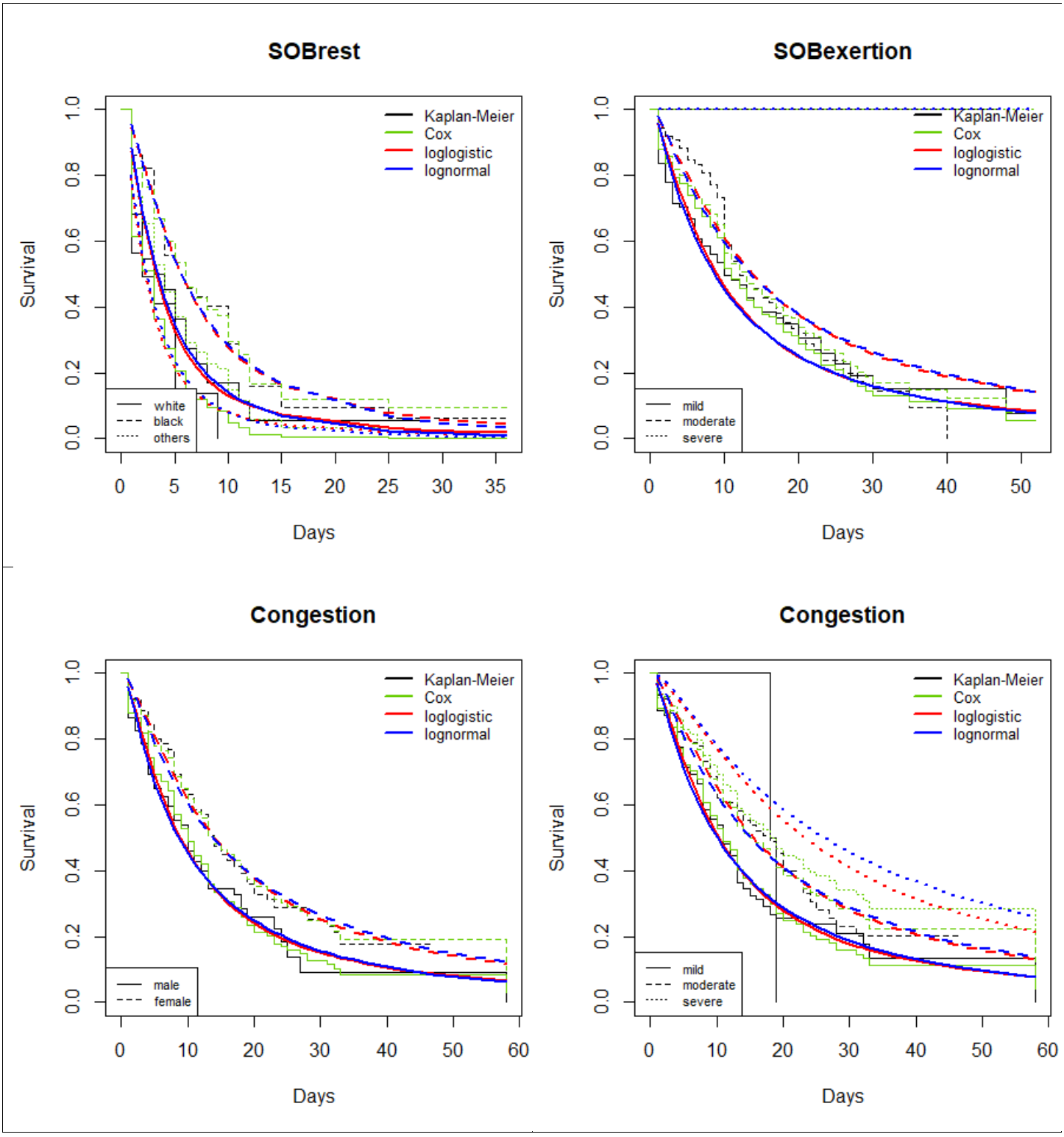
Figure 1 Survival curves for different models




Confusion
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
white
black
others
Cough
mild
moderate
severe
Fever
Diarrhea


Diarrhea
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
white
black
others
Dizzy
mild
moderate
severe
HA
JointPain
No Obesity
Obesity


LossSmellTaste
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
male
female
LossSmellTaste
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
No Immunesuppression
Immunesuppression
Nausea
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe
SOBrest
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
No Asthma
Asthma


SOBrest
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
white
black
others
SOBexertion
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe
Congestion
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
male
female
Congestion
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe

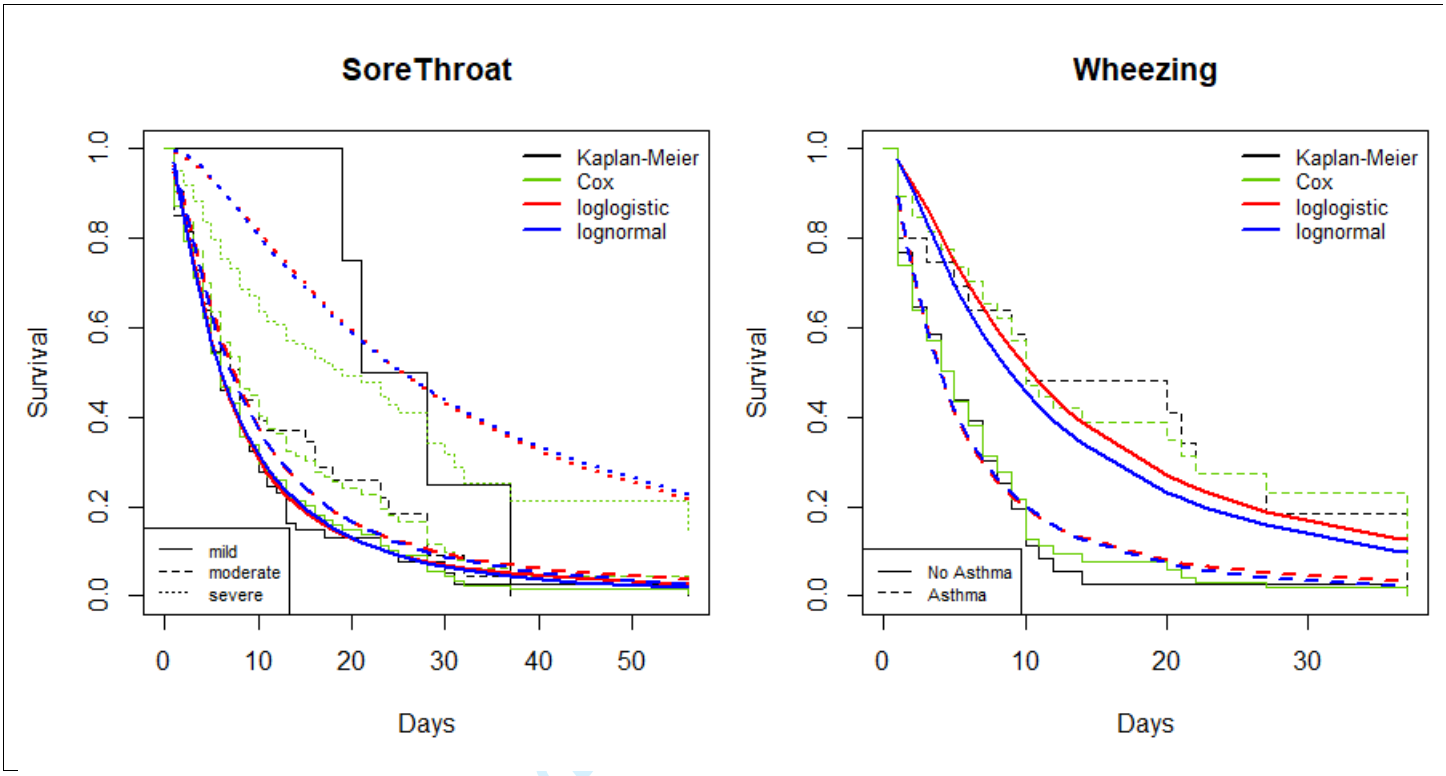
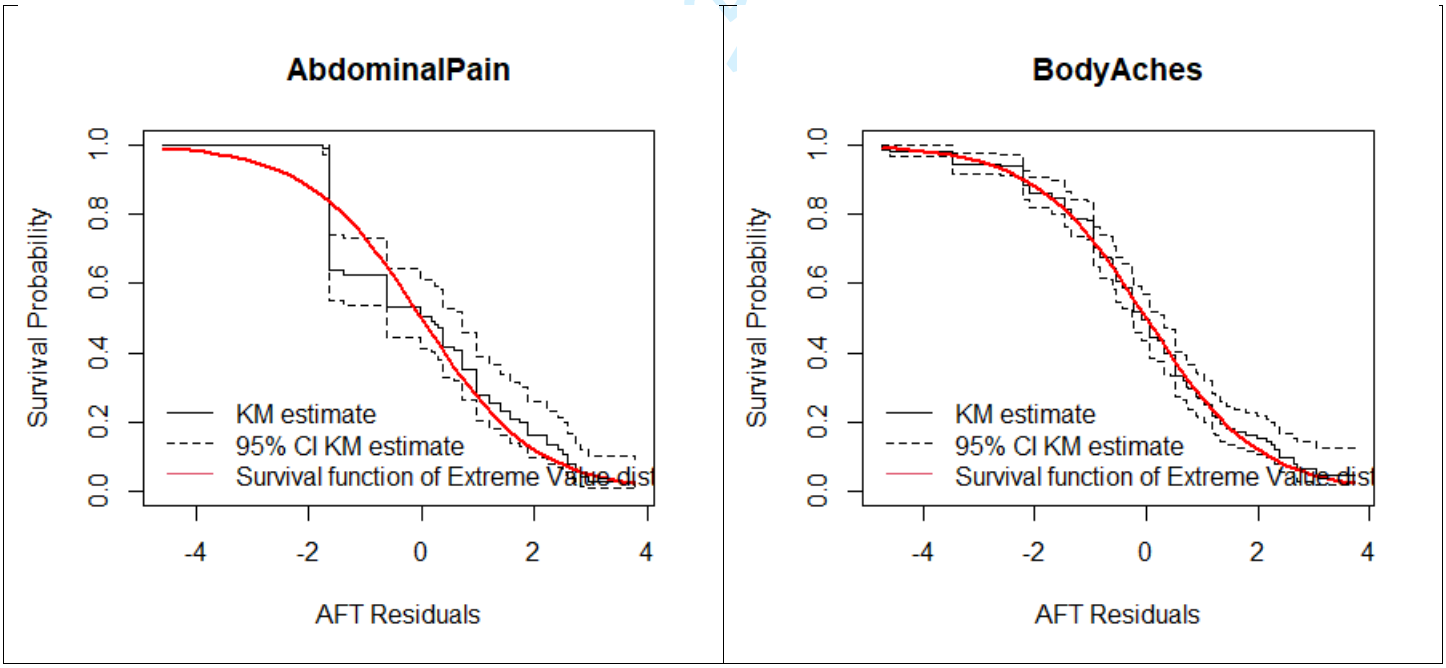
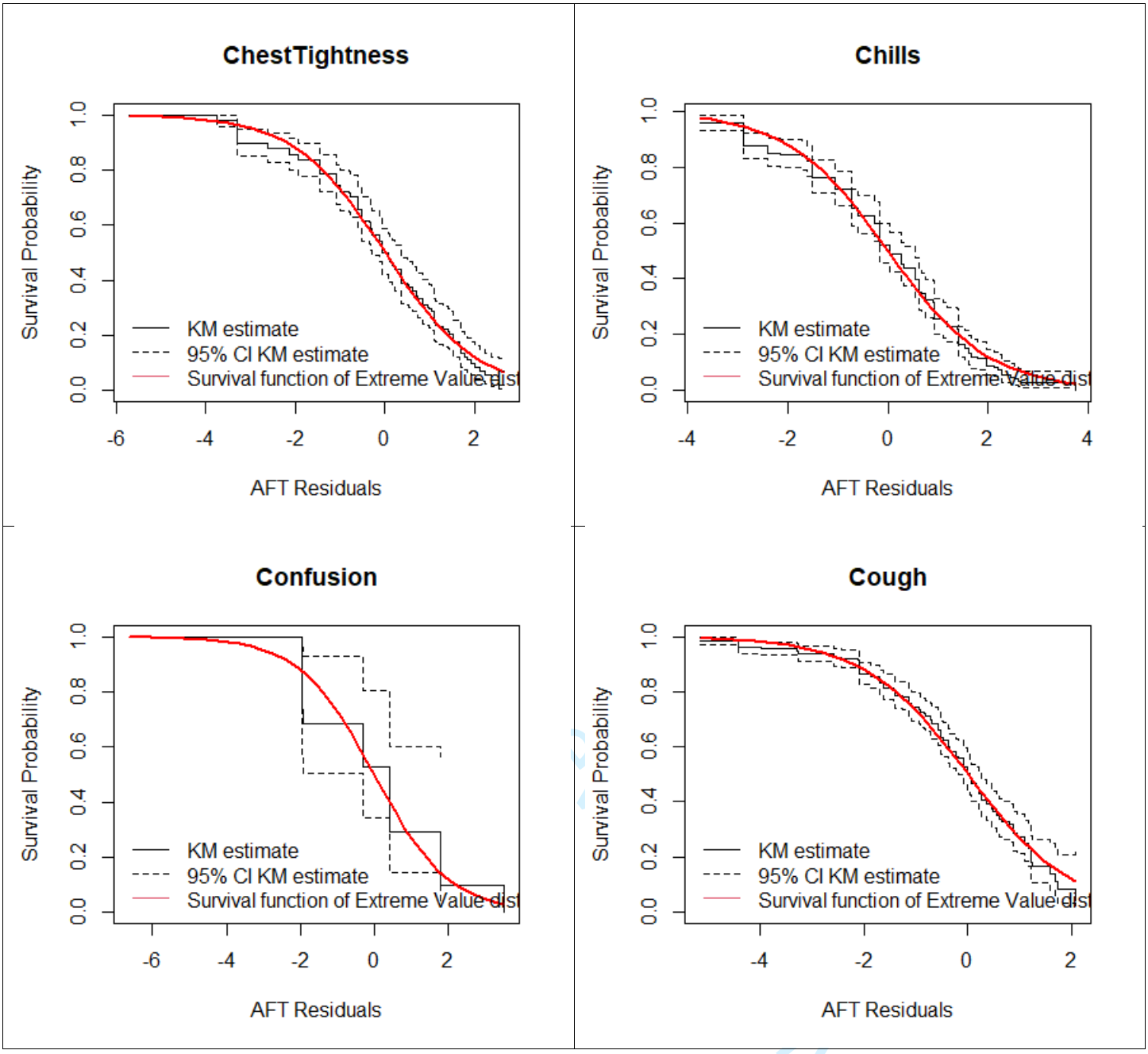
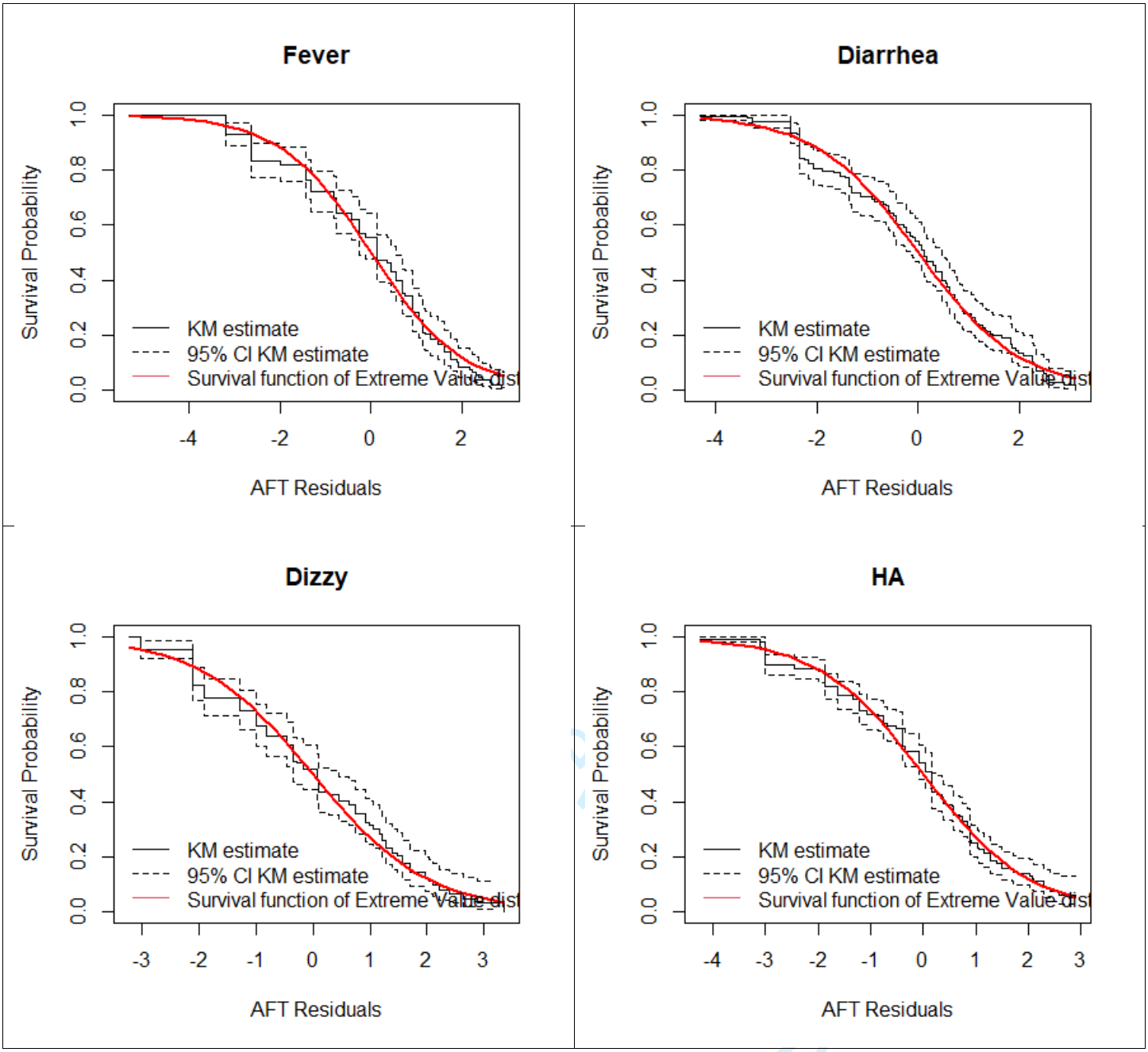
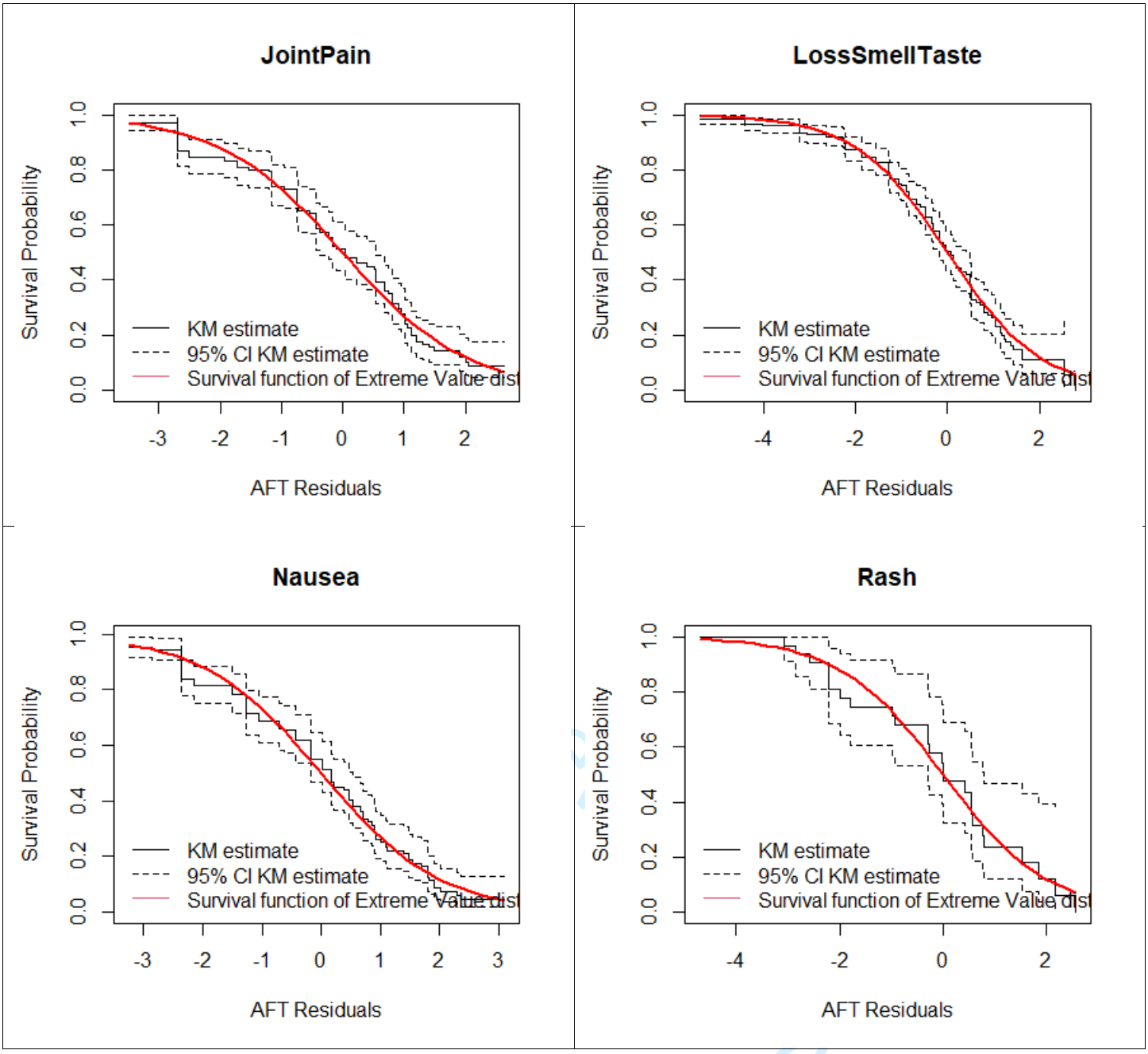


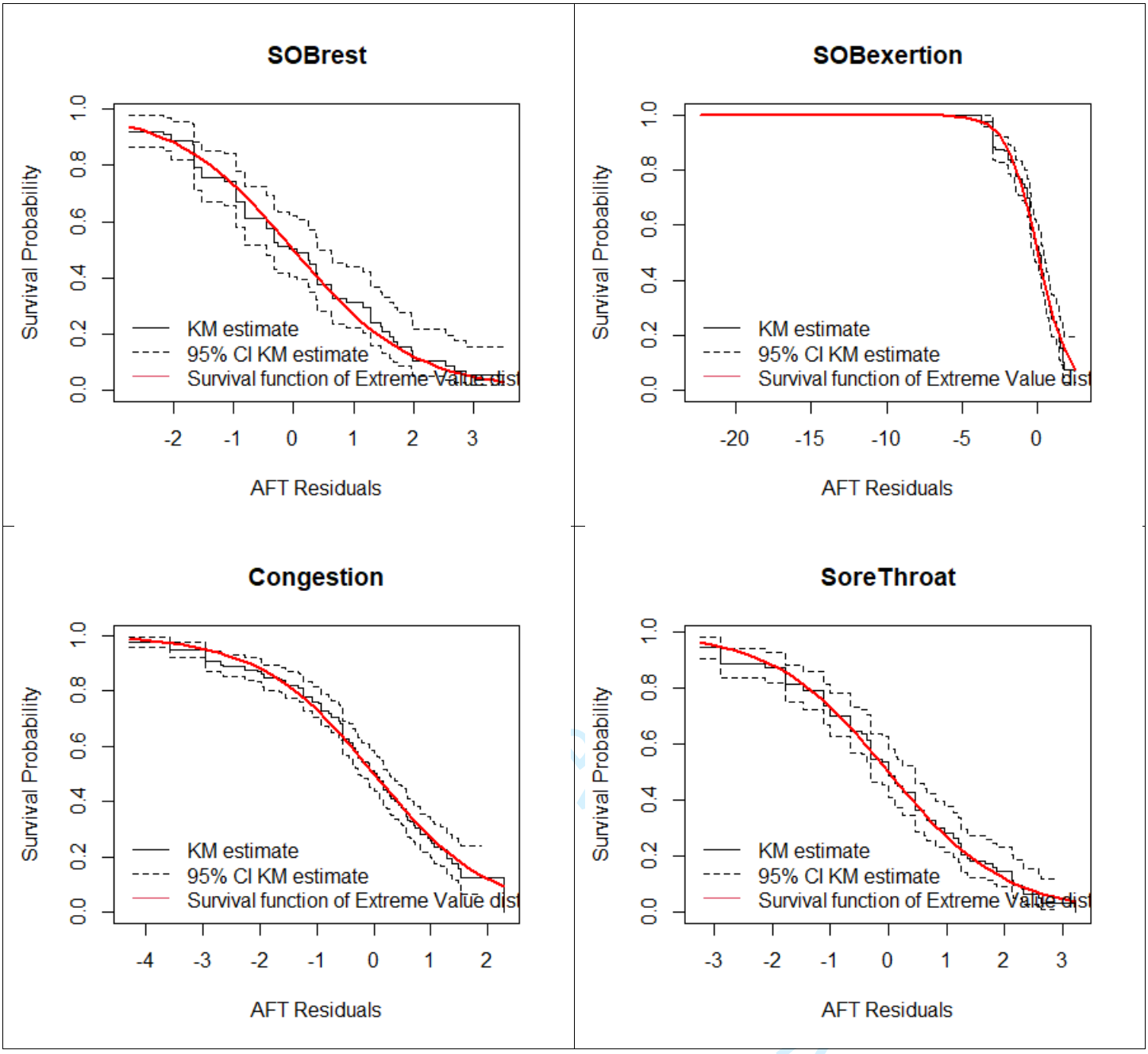

Figure 2a Goodness of fit, Kaplan Meier estimation of residual plotted against log-logistic distribution




ChestTightness
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-6
-4
-2
0
2
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
Chills
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-4
-2
0
2
4
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
Confusion
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-6
-4
-2
0
2
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
Cough
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-4
-2
0
2
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist


Fever
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-2
0
2
AFT Residuals
Diarrhea
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-2
0
2
AFT Residuals
Dizzy
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
3
AFT Residuals
HA
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-3
-2
-1
0
1
2
3
AFT Residuals


JointPain
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
AFT Residuals
LossSmellTaste
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-2
0
2
AFT Residuals
Nausea
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
3
AFT Residuals
Rash
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-2
0
2
AFT Residuals


SOBrest
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2
-1
0
1
2
3
AFT Residuals
SOBexertion
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-20
-15
-10
-5
0
AFT Residuals
Congestion
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-3
-2
-1
0
1
2
AFT Residuals
SoreThroat
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
3
AFT Residuals

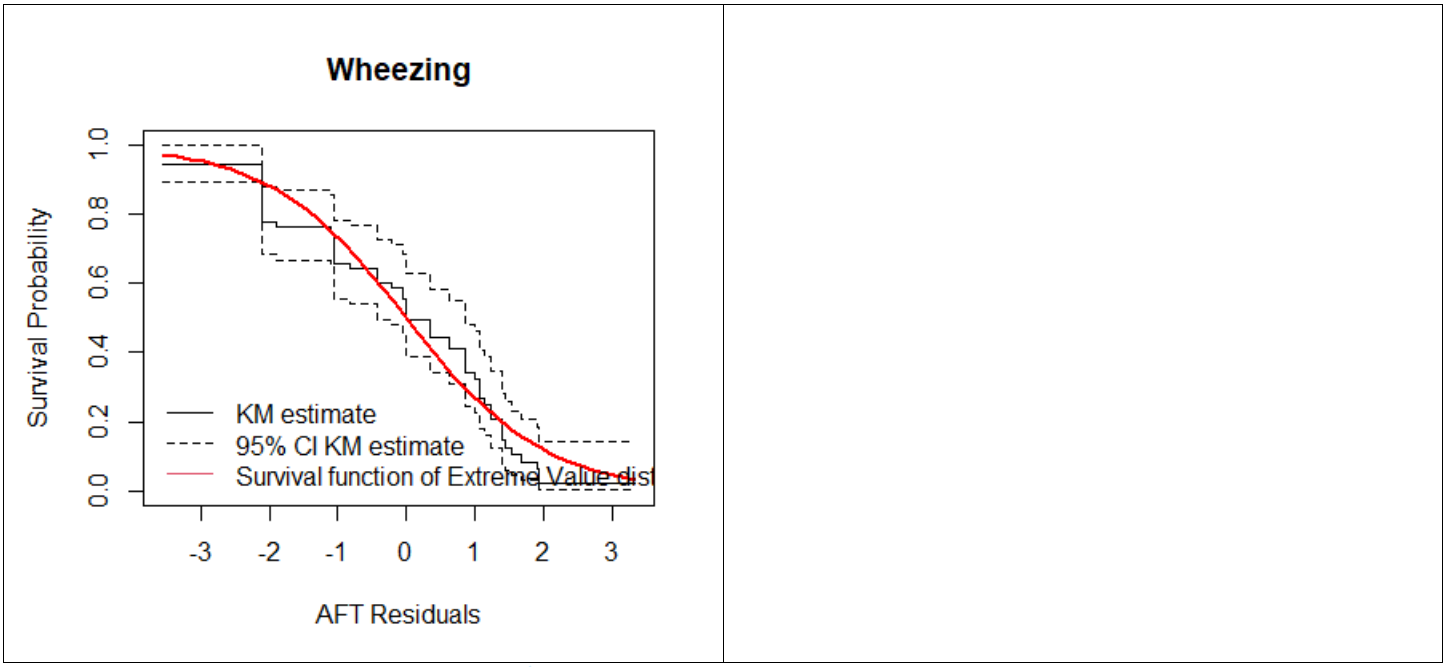
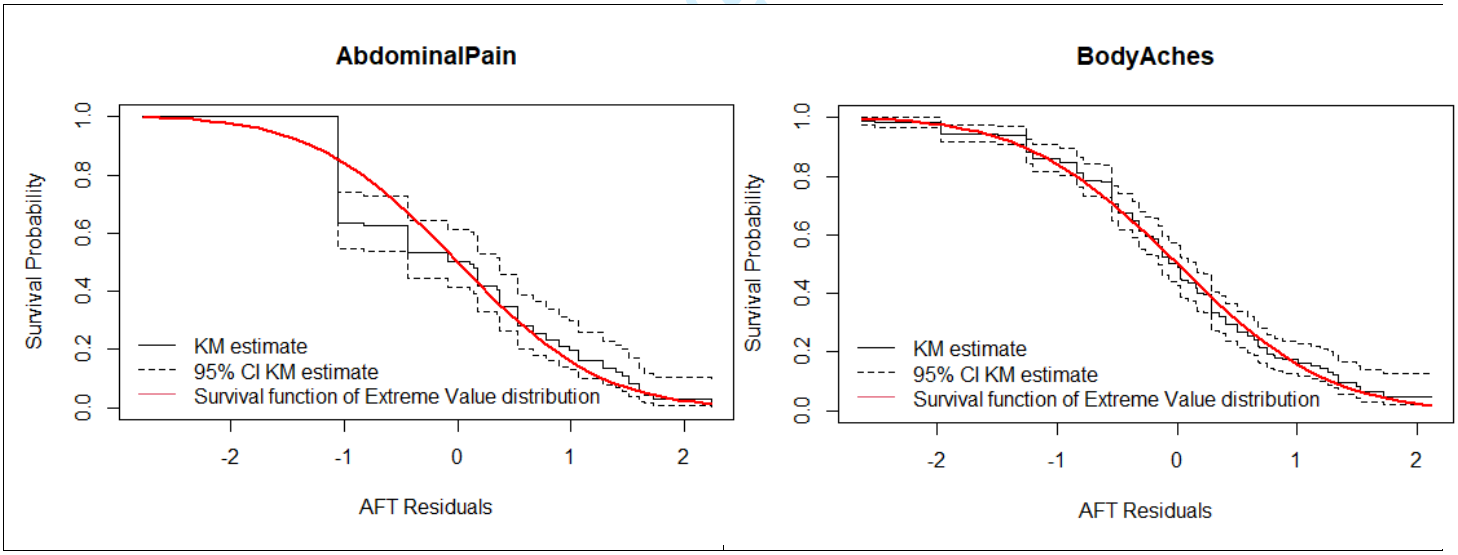
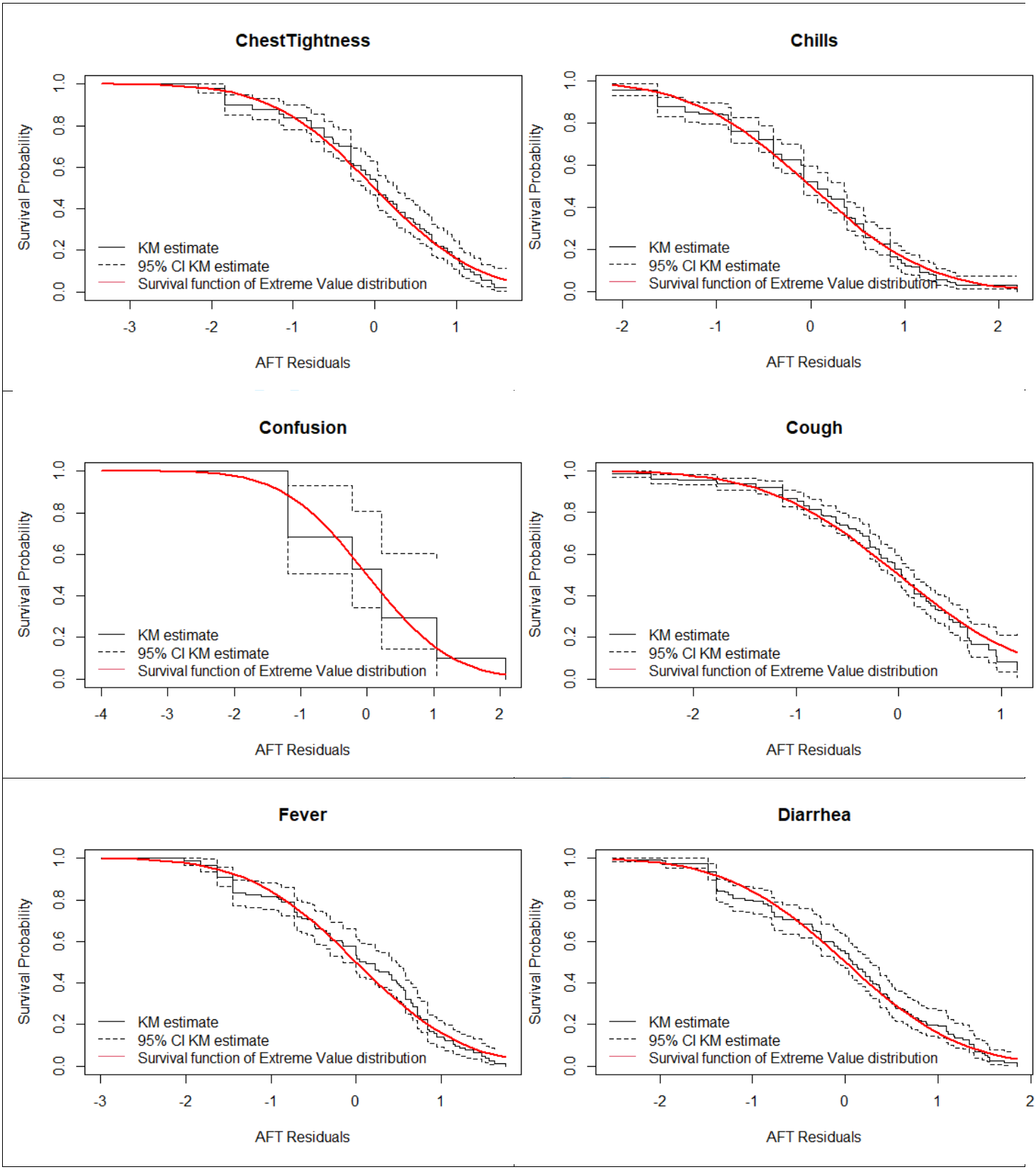
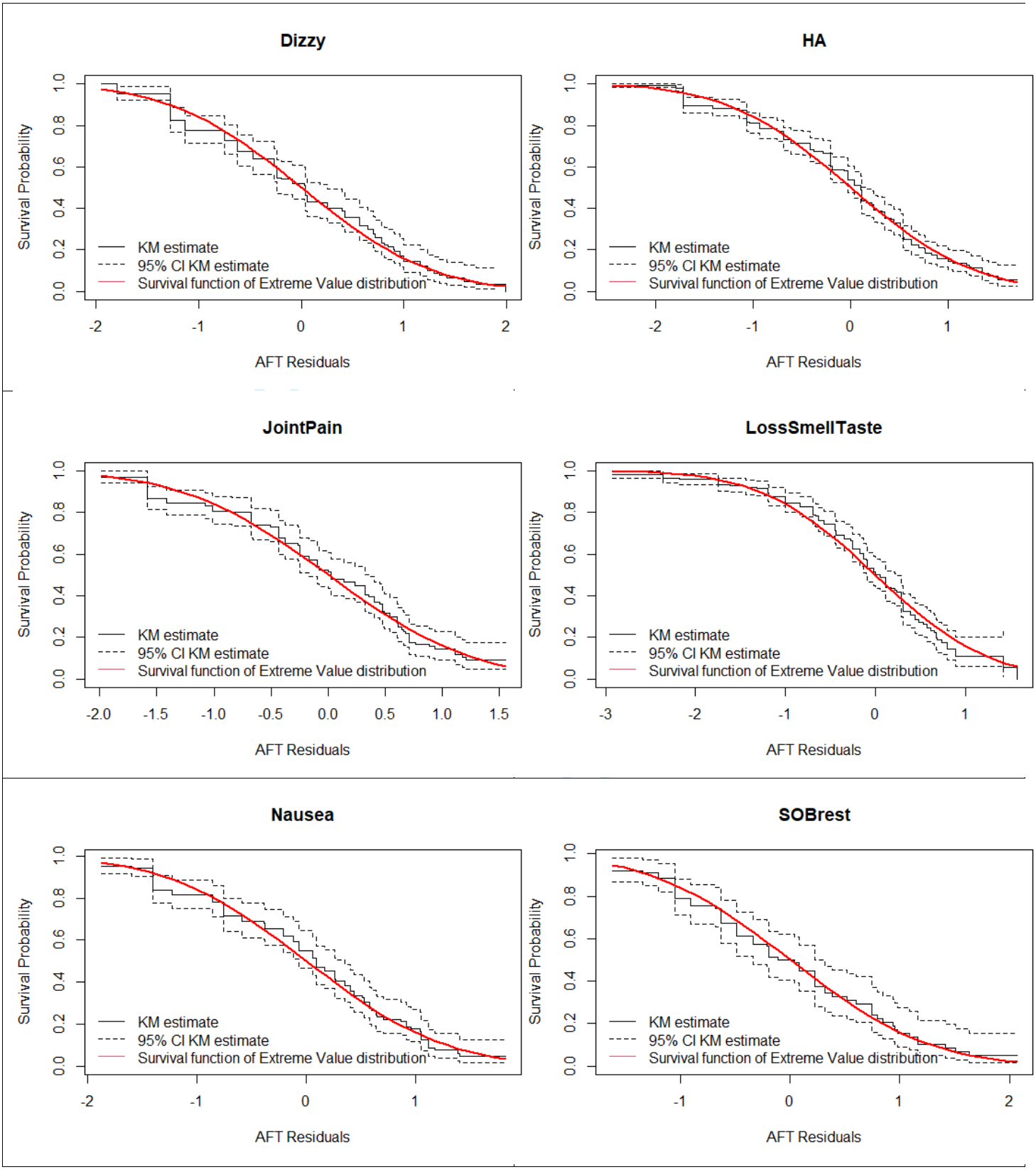
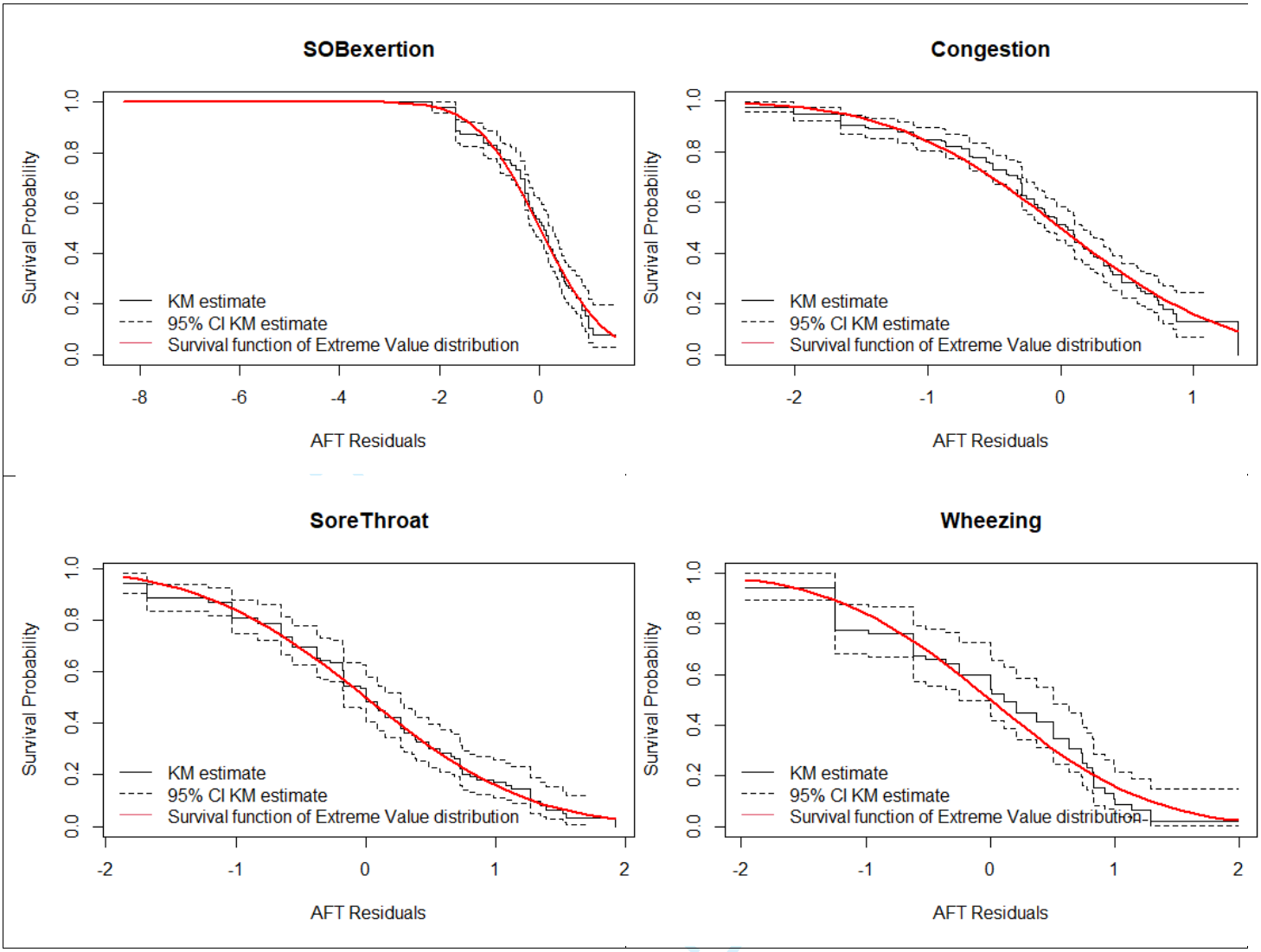



Figure 2b Goodness of fit, Kaplan Meier estimation of residual plotted against log-normal distribution




ChestTightness
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-3
-2
-1
0
1
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value distribution
Chills
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-2
-1
0
1
2
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value distribution
Confusion
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-4
-3
-2
-1
0
1
2
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value distribution
Cough
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-2
-1
0
1
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value distribution
Fever
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-3
-2
-1
0
1
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value distribution
Diarrhea
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
-2
-1
0
1
2
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value distribution


Dizzy
HA
JointPain
LossSmellTaste
Nausea
SOBrest
Survival Probability
AFT Residuals
KM estimate
95% CI KM estimate
Survival function of Extreme Value distribution



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract<br>(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1-2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4-5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>(*b*) For matched studies, give matching criteria and number of exposed and unexposed | 6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-10 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8-9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 10 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding<br>(*b*) Describe any methods used to examine subgroups and interactions<br>(*c*) Explain how missing data were addressed<br>(*d*) If applicable, explain how loss to follow-up was addressed<br>(*e*) Describe any sensitivity analyses | 10-11 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram | 12 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) Summarise follow-up time (eg, average and total amount) | 12-14 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 14-16 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 16 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 17-18 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 19-20 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 18-19 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 20 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | NA |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# Description of symptom course in a telemedicine monitoring clinic for acute symptomatic covid-19: a retrospective cohort study



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**Title:** Description of symptom course in a telemedicine monitoring clinic for acute symptomatic covid-19: a retrospective cohort study

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## ABSTRACT

**Objective:** Describe the disease course in a cohort of outpatients with covid-19 and evaluate factors predicting duration of symptoms

**Design:** Retrospective cohort study

**Setting:** Telemedicine clinic at a large medical system in Atlanta, Georgia

**Participants:** 337 patients with acute COVID-19. Exclusion criteria included intake visit more than 10 days after symptom onset and hospitalization prior to intake visit.

**Main outcome measures:** Symptom duration in days

**Results:** Common symptoms at intake visit are upper respiratory (73% cough, 55% loss of smell or taste, 57% sinus congestion, 32% sore throat), systemic (66% headache, 64% body aches, 53% chills, 30% dizziness, 36% fever). Day of symptom onset was earliest for systemic and upper respiratory symptoms (median onset day 1 for both), followed by lower respiratory symptoms (day 3, 95% CI 2-4), with later onset of gastrointestinal symptoms (day 4, 3 to 5), when present. Cough had the longest duration when present with median 17 days (15 to 21), with 42% not resolved at final visit. Loss of smell or taste had the second longest duration with 14 days (12 to 17), with 38% not resolved at final visit. Initial symptom severity is a significant predictor of symptom duration ($p<0.01$ for multiple symptoms).

**Conclusions:** Covid-19 illness in outpatients follows a pattern of progression from systemic symptoms to lower respiratory symptoms and persistent symptoms are common across categories. Initial symptom severity is a significant predictor of disease duration for most considered symptoms.

## Strengths and limitations of this study

Strengths:

- By systematically calling patients throughout acute illness, we are able to provide a visual representation of symptoms of acute illness in outpatients.
- Missing data are minimal during acute illness as patients are followed until symptom improvement.
- We used standardized templates for all patients and are able to analyze predictors of symptom duration for specific variables including age, comorbidities and symptom severity.

Limitations

- We are a single center study with limited patient numbers.
- We do not follow patients until disease resolution and cannot define an end date for all symptoms.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Covid-19 symptoms in non-hospitalized adults span multiple organ systems, most often including respiratory and systemic symptoms

Symptom duration varies substantially between patients, ranging from brief (days) to prolonged (weeks to months)

WHAT THIS STUDY ADDS

Disease duration is predicted by the severity of initial symptoms during the acute illness

Disease course can be described in a pattern with early systemic symptoms, followed by lower respiratory and, less often, gastrointestinal symptoms

Multiple symptoms may persist to 30 days, most often cough, loss of smell or taste, sinus congestion, shortness of breath on exertion, body aches, and headache

## INTRODUCTION

Coronavirus disease 2019 (covid-19) has brought large numbers of patients to medical attention within a span of months for care of a previously undescribed illness. Early reports on the presentation and natural history of covid-19 appropriately focused attention on the severe cases and critically ill.[1-5] Subsequent surveillance has demonstrated that the majority of patients have milder forms of illness[6] and it is recommended that they remain at home with medical supervision.[7,8] Although the duration of home isolation is defined based on symptoms,[7] understanding of the symptom course of outpatients with covid-19 is limited and most reports include presenting symptoms alone or cross-sectional follow-up information.[9-18] Predictors of individual symptom duration have not been described.

In March 2020, we established a virtual clinic for the care of patients in home isolation with covid-19: the “Virtual Outpatient Management Clinic” (VOMC), using available knowledge for assessment and treatment guidelines. All patients underwent VOMC intake visits with a physician or advanced practice provider (APP), including assessment of specific covid-19 symptoms using a standardized clinical note. Patients were followed for symptom management with regular telephone calls by registered nurses (RNs) and APPs until improvement or hospitalization. Subsets from this cohort have been reported elsewhere in a small case series[19] and for hospitalization risk prediction;[20] the current study is the first to analyze complete longitudinal symptom reporting for the cohort.

As it became clear in clinical practice that symptom duration varies substantially between patients, we undertook this study to determine the predictors of the symptom course of our VOMC cohort. We hypothesized that a combination of demographics, comorbidities, and initial symptom severity would predict symptom duration.

## METHODS

### Study setting

The study was a retrospective cohort study, conducted at Emory Healthcare, the largest academic health system in Georgia (serving the greater Atlanta metropolitan area), which includes more than 250 provider locations and 120 primary care locations. The VOMC comprised an intake team of 14 physicians and 3 APPs from two primary care clinics; and follow-up call teams included 19 redeployed registered nurses (RNs) and 20 APPs. All intake providers were trained in the use of the risk assessment tool in a one-hour webinar and conducted a median of 25 intake visits during the study period (range: 5-99), with the majority of intake visits conducted by physicians (83.6%).

### Study cohort

We included outpatient adults who completed their VOMC intake visit between 24 March 2020 and 26 May 2020 with initial symptom dates between 17 March and 20 May. We excluded patients hospitalized prior to the intake visit and patients with an

intake visit occurring more than 10 days after symptom onset in order to improve the accuracy of early symptom reporting.

During the study period, outpatient covid-19 testing was conducted by medical providers using nasopharyngeal sampling for real-time reverse transcription–polymerase chain reaction (RT-PCR) detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Testing of outpatients occurred primarily at a screening clinic (converted outpatient clinical space) and did not include a clinical assessment except for triage of visibly unstable patients. As test volume increase in April 2020, a drive-through site was added (accounting for 27% of VOMC referrals during the study period). Patients requiring in-person evaluation could be triaged at any time in their illness to the emergency department (ED) or a lower acuity “in-person” Acute Respiratory Clinic (ARC), described elsewhere.[21] During the study period, 12% of VOMC patients were seen in the ARC (either for initial diagnosis or evaluation of symptoms).

Adult patients with positive RT-PCR results from the outpatient sites or emergency departments were called by a result notification team to provide isolation advice and refer to the VOMC. All patients with positive RT-PCR were offered VOMC referral during the study period. The criteria for testing and details of care are outlined in Box 1. During the VOMC intake visit, symptom severity was assessed by the provider using criteria in Box 1 as well as self-reported by the patient.

BOX 1: Virtual Outpatient Management Clinic (VOMC) care during study period

**Outpatient covid-19 testing criteria (March-April 2020):**

1. Symptom(s): either (a) fever, cough, or shortness of breath or (b) two symptoms from the following: sore throat, congestion, myalgias, fatigue, diarrhea, loss of smell.

2. Prioritize: (a) frontline healthcare workers, (b) students on-campus and health professions, (c) CDC employees, (d) patients with risk factors (age, comorbidity, immunosuppression, work in a communal setting).
3. Setting: outpatient clinic repurposed as testing site (12 March 2020) and additional drive-through site added to expand capacity (9 April 2020).

**Emergency Department covid-19 testing criteria (March 2020):**

1. Symptom(s): cough, fever, sore throat, or shortness of breath.
2. Prioritize: (a) severe illness (difficulty breathing or other indication for admission), (b) high risk comorbidities including chronic lung disease, heart disease, chronic kidney disease, diabetes, immunocompromising conditions, or (c) communal housing or living with high-risk individual.

**Acute Respiratory Clinic in-person care site (April-May 2020):**

1. Referrals for evaluation (and testing if needed) from sources: covid-19 hotline (triage of incoming patient calls), physician offices, and VOMC for in-person evaluation of VOMC patients.
2. Testing criteria: none specified, at provider discretion only.
3. Setting: primary care clinic repurposed as acute care site for respiratory complaints (known or possible covid-19), with services including phlebotomy, plain radiography, EKG, pulse oximetry. Staffed daily by 1-2 physicians and APPs from the General Internal Medicine and one Infectious Disease specialist.

**VOMC enrollment criteria:**

1. Diagnosis of covid-19 by nasopharyngeal PCR, and
2. Requesting* outpatient monitoring and/or management of covid-19 symptoms.
3. Able to complete telemedicine intake (synchronous audio/video connection by smartphone or computer preferred), with telephone-only visit as backup option.

*All patients with positive results were notified by telephone and offered VOMC referral.

**Intake VOMC visit:**

1. Documentation template includes symptom history, symptom severity (patient-reported and provider-assessed), past medical history, physical examination and risk assessment.
2. Symptoms assessed: “systemic” (fever, chills, body aches, dizziness, headache, joint pain), “upper respiratory” (loss of smell or taste, sinus congestion, sore throat, cough), “lower respiratory” (chest tightness, shortness of breath with exertion, shortness of breath at rest, wheezing), “gastrointestinal” (abdominal pain, nausea, diarrhea), as well as confusion and rash. Note: symptoms assessed as a single list and not grouped into categories during assessment.
3. Provider gives advice for (1) symptom management, (2) home isolation guidance and (3) outpatient monitoring.

**Provider-assessed symptom severity definition (at VOMC intake visit):**

1. Mild
    a. Respiratory: Cough, sputum production
    b. Systemic: Fever, chills, malaise, myalgia, anorexia, diarrhea, vomiting, headache
2. Moderate
    a. Respiratory: Severe cough, dyspnea on exertion, wheezing or sensation of mid-chest tightness
    b. Systemic: N/A (Not provided in VOMC clinical guideline)
3. Severe
    a. Resting dyspnea, labored breathing, resting pulse oximetry ≤92%, pleuritic pain, hemoptysis
    b. Systemic: acute confusion, severe weakness, syncope, acute decline in functional status

**Follow-up phone calls (March-June 2020):**

1. Patients receive VOMC follow-up telephone calls based on hospitalization risk tool[20] that includes age, comorbidity, symptom severity, and social support:
    a. Low risk: every other day for a minimum of 7 days from symptom onset
    b. Intermediate risk: daily for a minimum of 14 days from symptom onset
    c. High risk: twice daily for a minimum of 21 days from symptom onset
2. All patients called until the intervals above and for a minimum 3 days after improvement in fevers (without antipyretics) and improvement in respiratory symptoms (whichever criteria was longer).

3. Patients with improving or worsening symptoms could change risk level after enrollment at provider discretion.

**Data sources**

Study data were obtained from two specific provider note types deployed in March 2020 within the Emory Healthcare electronic health record (Cerner Corp., Kansas City, Missouri, United States): (1) VOMC provider intake visit and (2) VOMC follow-up telephone call. The intake visit assessment note template included (1) documentation of specific covid-19 symptoms including onset and offset dates, (2) patient reported and provider-assessed symptom severity, and (3) documentation of specific medical conditions associated with risk of severe covid-19 (based on medical literature search in March 2020). The VOMC follow-up telephone call template included an identical symptom list with "yes/no" selection for documentation of the presence or absence of symptoms at follow-up.

If symptom onset date was not identified in VOMC notes, we conducted manual chart review of telephone records prior to VOMC enrollment. Additional demographic information including age, gender, and race (if recorded) was included from the electronic health record.

To ensure that symptoms were counted only once a day per patient among patients receiving 2 calls per day, if a symptom was listed as present more than once for a particular day, it was counted only once. Among patients receiving calls every other

day, if a symptom was present on both the preceding and subsequent day it was listed as present on the single non-call day in between for symptom duration.

**Main outcomes**

To create a visual representation of overall disease as a heatmap, we define day 1 as the first day a patient had any symptom and each individual symptom is counted only on days present.

The main outcome was duration in days for each specific symptom, using the first and last documented dates a symptom was present. Because patients could be discharged from VOMC with ongoing symptoms, if a symptom was present on the last nurse phone call it was considered censored for survival analysis. If a symptom was not present on the last nurse phone call, then the symptom was considered resolved.

The secondary outcome was the day of symptom onset. Symptoms were grouped into systems: upper respiratory (cough, congestion, sore throat, loss of smell or taste), systemic (fever, body aches, chills, dizziness, headache, joint pain), lower respiratory (shortness of breath with exertion, shortness of breath at rest, chest tightness, wheezing) and gastrointestinal (nausea, abdominal pain, diarrhea). Confusion and rash were not included into symptom groups. For initial symptom severity, we used the provider-assessed severity at the intake visit (criteria listed in Box 1). If provider-assessed severity was not available (n=25) then the patient-reported severity at intake

visit was used (n=18 mild and n=7 moderate). Clinical record extraction was conducted 21 June 2020 at which time all enrolled patients had at least 30 days of follow up based on symptom start date and all patients had received their final VOMC nurse call.

**Potential bias**

Testing criteria are noted in Box 1. Healthcare employees were prioritized in the outpatient screening process and may be overrepresented in the cohort. Testing in the emergency department prioritized patients with more severe symptoms and likely underrepresented mild disease. Furthermore, patient enrollment in VOMC was voluntary at the time of results notification, which may result in selection bias. Patients were scheduled for the minimum recommended follow-up calls at the time of intake (and could later extend care further if needed) but could disengage on request, which could lead to attrition bias.

**Predictors**

Demographics, comorbidities, and initial symptom severity were tested as predictors of symptom duration.

**Statistical analysis**

Survival analysis was used to analyze symptom start date by system and duration of individual symptoms. Kaplan-Meier curves were constructed for symptom onset (grouped by systems) to calculate median day of onset with pairwise log-rank test used to compare the system groupings. Kaplan-Meier curves were also used to determine

the median duration for each symptom. Cox proportional hazard models were constructed but the proportional hazards requirement was not met for several covariate symptom combinations so Cox models were not used. Time-varying covariates can be included as strata but different baseline hazards are modeled for each strata so the effect of the strata covariate is not estimated.[22] Cox models with time-by-covariate interactions are difficult to interpret and are included in the supplement (supplement table 1).

Subsequent analysis showed accelerated failure time (AFT) models had a better fit. AFT models are an alternate method of survival analysis which is parametric and does not require proportional hazards. To decrease the chance of false positive findings we screened each comorbidity to see if it was a significant predictor of symptom duration with symptom duration analyzed as strata (supplement table 2). Models were developed for each symptom including the covariates that were significant (gender, initial symptom severity, asthma, immunosuppression, obesity) to the $p<0.001$ level and race. Statistically significant covariates for each symptom's model were retained in the final AFT models. The Akaike information criterion (AIC) showed the AFT models were a better fit than the Cox proportional hazards models (supplement table 3). Log-normal and log-logistic distribution AFT models appeared to fit the data the best with very similar results (supplement table 4), and we present the log-logistic distribution model in this paper with projected survival curves for different models in supplement figure 1. Goodness-of-fit testing was performed for the log-normal and log-logistic AFT models (supplement figure 2). Self-reported symptom severity was used if provider-assessed

symptom severity was missing (n=25). This resulted in a similar goodness of fit compared to imputing the missing provider assessed severity (supplement table 5). Statistical analysis was performed using RStudio version 4.0.3 packages survival and flexsurv (R core Team, 2020).

**Patient and public involvement**

Patients and the public were not involved in the design and conduct of the study, outcomes, recruitment, or planned dissemination.

**RESULTS:**

There were 551 intake visits completed in the VOMC between 24 March 2020 and 26 May 2020. We included 337 patients in the study after excluding: 198 patients with VOMC intake visit more than 10 days after symptom onset, 6 patients without documented positive RT-PCR test for SARS-CoV-2, 3 patients hospitalized prior to VOMC enrollment, 3 patients with blank or uninterpretable symptom entries and 4 patients with neither provider nor self-reported initial symptom severity. Of the included patients, 33 (10%) were subsequently hospitalized and seven of the hospitalized patients resumed VOMC care after hospital discharge.

The testing location for included patients was primarily outpatient (n=304, 90%), followed by ED (n=33, 10%). During the study period (testing dates 15 March 2020 to 22 May 2020), the following number of patients tested positive for SARS-CoV-2 by RT-

PCR at Emory Healthcare: 730 in the outpatient setting, 170 in the ED, 740 in the inpatient setting, 1 in ambulatory surgery and 1 patient in hospice.

**Characteristics of the study population**

Table 1 describes demographics, comorbidities, and symptoms recorded at the VOMC intake visit for the cohort grouped by initial symptom severity. Our study population had a mean age of 45.7 years, 68% women, and 52% black. The mean number of days from symptom onset to VOMC intake visit was 5.8 days, with follow-up phone calls continuing until mean symptom day 19. There was a significant difference in the initial symptom severity by patient age. Asthma, heart failure, and hypertension were significantly different (P<0.05) between the initial symptom severity groups. Only eight patients had severe initial symptoms severity and four (50%) were hospitalized during care. Of the four nonhospitalized patients in the severe symptom group, two were evaluated by the ARC and determined to be stable for outpatient monitoring and two were managed by the VOMC telemedicine team alone without escalation to in-person care.



Table 1 Demographics, comorbidities and symptoms at VOMC intake visit

| | Initial symptom severity | | | | Anova p value |
|---|---|---|---|---|---|
| | Total (n=337) | Mild (n=223) | Moderate (n=106) | Severe (n=8) | |
| Demographics: | | | | | |
| Age, mean (95% CI) | 45.7 (44.1-47.2) | 44.6 (42.2-45.9) | 48.1 (45.5-60.9) | 57.9 (44.8-71.0) | 0.003 |
| Symptom onset to first VOMC visit (days, 95% CI)* | 5.8 (5.5-6.0) | 5.7 (5.3-6.0) | 6.0 (5.6-6.4) | 5.6 (4.1-7.1) | 0.508 |
| Symptom onset to last phone call (days, 95% CI)† | 19.0 (18.0-20.0) | 17.3 (16.2-18.4) | 22.5 (20.5-24.6) | 19.9 (6.3-33.5) | <0.001 |

| Count, (%) | | | | | Chi$^2$ p value |
|---|---|---|---|---|---|
| Gender, men | 108 (32%) | 74 (33%) | 34 (32%) | 0 (0%) | 0.142 |
| Gender, women | 232 (68%) | 149 (67%) | 72 (68%) | 8 (100%) | |
| Race, white | 59 (17%) | 38 (17%) | 19 (18%) | 2 (25%) | 0.397 |
| Race, black | 177 (52%) | 112 (50%) | 56 (53%) | 6 (75%) | |
| Race, other/unknown | 104 (31%) | 73 (33%) | 31 (29%) | 0 (0%) | |
| Comorbidities: | | | | | |
| Age>=60 | 61 (18%) | 35 (16%) | 24 (23%) | 2 (25%) | 0.272 |
| Alcohol abuse/addiction | 4 (1%) | 2 (1%) | 2 (2%) | 0 (0%) | 0.699 |
| Asthma | 43 (13%) | 19 (9%) | 22 (21%) | 2 (25%) | 0.005 |
| Cancer or malignancy | 24 (7%) | 17 (8%) | 6 (6%) | 1 (13%) | 0.678 |
| Confirmed pregnant | 1 (0.3%) | 1 (0.4%) | 0 (0%) | 0 (0%) | 0.774 |
| COPD | 2 (1%) | 0 (0%) | 2 (2%) | 0 (0%) | 0.112 |
| Coronary artery disease | 9 (3%) | 5 (2%) | 4 (4%) | 0 (0%) | 0.646 |
| Diabetes | 48 (13%) | 26 (12%) | 19 (18%) | 3 (38%) | 0.051 |
| Drug abuse/addiction | 3 (1%) | 2 (1%) | 1 (1%) | 0 (0%) | 0.963 |
| Heart failure | 3 (1%) | 1 (0.4%) | 1 (1%) | 1 (13%) | 0.002 |
| Hypertension | 110 (33%) | 64 (29%) | 41 (38%) | 6 (75%) | 0.009 |
| Immune suppression | 17 (5%) | 7 (3%) | 9 (8%) | 1 (13%) | 0.073 |
| Lung disease | 8 (2%) | 3 (1%) | 5 (5%) | 0 (0%) | 0.155 |
| Obesity (BMI > 30) | 100 (30%) | 60 (27%) | 36 (34%) | 4 (50%) | 0.189 |
| Renal disease | 8 (2%) | 4 (2%) | 3 (3%) | 0 (0%) | 0.758 |
| Symptom present prior to or at intake Visit | | | | | |
| Current fever | 121 (36%) | 66 (30%) | 51 (48%) | 4 (50%) | 0.003 |
| Chills | 180 (53%) | 102 (46%) | 72 (68%) | 6 (75%) | <0.001 |
| Body aches | 216 (64%) | 127 (57%) | 83 (78%) | 6 (75%) | 0.001 |
| Dizziness when standing | 102 (30%) | 47 (21%) | 51 (48%) | 4 (50%) | <0.001 |
| Confusion | 10 (3%) | 4 (2%) | 4 (4%) | 2 (25%) | 0.001 |
| Headache | 221 (66%) | 141 (63%) | 74 (70%) | 6 (75%) | 0.427 |
| Loss of smell or taste | 187 (55%) | 114 (51%) | 66 (62%) | 7 (88%) | 0.030 |
| Sinus congestion | 192 (57%) | 122 (55%) | 65 (61%) | 5 (63%) | 0.501 |
| Sore throat | 108 (32%) | 70 (31%) | 35 (33%) | 3 (38%) | 0.905 |
| Cough | 247 (73%) | 149 (67%) | 91 (86%) | 7 (88%) | 0.001 |
| Chest tightness | 110 (33%) | 55 (25%) | 49 (46%) | 6 (75%) | <0.001 |
| SOB at rest | 46 (14%) | 19 (8%) | 22 (21%) | 5 (63%) | <0.001 |
| SOB with exertion | 122 (36%) | 48 (22%) | 68 (64%) | 6 (75%) | <0.001 |
| Wheezing | 43 (13%) | 20 (9%) | 22 (21%) | 1 (13%) | 0.011 |
| Abdominal pain | 53 (16%) | 27 (12%) | 25 (24%) | 1 (13%) | 0.027 |
| Nausea | 82 (24%) | 32 (15%) | 45 (42%) | 5 (63%) | <0.001 |
| Diarrhea | 112 (33%) | 62 (28%) | 48 (45%) | 2 (25%) | 0.006 |

| | | | | | |
|---|---|---|---|---|---|
| Joint pain | 94 (28%) | 44 (20%) | 47 (44%) | 3 (38%) | <0.001 |
| Rash | 13 (4%) | 6 (3%) | 6 (6%) | 1 (13%) | 0.187 |

COPD=chronic obstructive pulmonary disease; SOB=shortness of breath; VOMC=virtual outpatient management clinic

*Number of days from initial symptom(s) of covid-19 to completion of telemedicine intake visit for the Virtual Outpatient Management Clinic (VOMC), inclusive of time required for testing, result notification, and scheduling with VOMC.

†Number of days from initial symptom(s) of covid-19 to the final telephone call with VOMC. The calls would end with patient-reported symptom improvement (not necessary resolution) or hospital admission.



**Symptoms at VOMC intake visit**

The most frequently reported symptoms occurring prior to and at the time of the VOMC intake visit included: 73% cough, 66% headache, 64% body aches, 57% sinus congestion, 55% loss of smell or taste, and 53% chills (table 1). All symptoms within the systemic, lower respiratory, and gastrointestinal systems were significantly different between severity groups. The only symptoms that were not significant were headache, sinus congestion, sore throat, and rash.

**Time course of individual symptoms**

Figure 1a displays heat maps of symptoms for 304 patients, presenting the daily percentage of patients with specified symptoms over a 30 day follow up period. The 33 patients hospitalized after VOMC intake are not included in figure 1 because daily symptom data were not collected during hospitalizations. Among symptoms included in this visual, the highest daily prevalence reported during 30 days of follow up was for cough (60%), loss of smell or taste (50%), sinus congestion (46%), body aches (46%), and headache (45%).. The most frequent remaining symptoms at 30 days were cough

(5%), body aches (4%), sinus congestion (3%), and shortness of breath with exertion (3%). Fever was not a prominent symptom during 30 days of follow up, with peak daily prevalence of 22% in the first two days of illness.

**Time course of symptoms by initial symptom severity**

The heat map findings for mild initial symptom severity group (n=209 for heat map) demonstrate similar rates of initial upper respiratory symptoms compared to the entire heat map cohort, with peak daily prevalence of cough in 52% and sinus congestion in 45% during the first week (figure 1b). Rates of lower respiratory symptoms were lower (e.g. shortness of breath with exertion in 20% on day 8, vs 30% in overall cohort). Rates of persistent symptoms at 30 days were lower in the mild initial symptom severity cohort, with no more than 1% reporting persistence of each individual symptom.

The heat map for moderate initial symptom severity (figure 1c, n=91) had higher rates of all symptoms (compared to overall group and mild initial symptom severity). Differences were less for upper respiratory symptoms such as sinus congestion (peak prevalence 54% in moderate group compared with 46% overall) and greater for lower respiratory symptoms (e.g. shortness of breath with exertion 56% vs 30%), systemic symptoms (e.g. joint pain 36% vs 18%), and gastrointestinal symptoms (e.g. diarrhea 36% vs 21%). At 30 days the most frequent symptoms remaining were cough (9%), sinus congestion (8%), body aches (8%), joint pain (6%), loss of taste or smell (5%), shortness of breath with exertion (5%), and headache (4%).

There were too few nonhospitalized patients with severe initial symptom severity (n=4) to represent with a heatmap. This group had high prevalence (100% within the first week) of chills, body aches, loss of smell or taste, sore throat, cough, chest tightness, and shortness of breath with exertion. At 30 days, 3 patients (75%) still had cough and shortness of breath with exertion.

**Timing of symptom onset of by system**

The median day of symptom onset determined by Kaplan-Meier curves is shown in table 2. The onset for systemic and upper respiratory symptoms frequently occurred on day 1, with gastrointestinal and lower respiratory symptoms occurring later. Recognizing that cough can be a manifestation of upper airway or lower airway infections, we analyzed cough separately, finding a median start of 1 day (95% confidence interval 1 to 1). This was not different from the median start day for upper respiratory symptoms (p=0.253), but it was significantly different than the median start day for lower respiratory symptoms (p<0.001) so we grouped cough with the upper respiratory system.

Table 2 Median day of symptoms onset by system determined from Kaplan-Meier curves

| System | median (95% CI) | p value | | |
|---|---|---|---|---|
| | | vs Systemic | vs Upper | vs Lower |
| Systemic | 1 (1-1) | n/a | 0.032 | p<0.001 |
| Upper | 1 (1-1) | 0.032 | n/a | p<0.001 |
| Lower | 3 (2-4) | p<0.001 | p<0.001 | n/a |
| Gastrointestinal | 4 (3-5) | p<0.001 | p<0.001 | 0.306 |

Systemic=fever, body aches, chills, dizziness, headache, joint pain; Upper=cough, congestion, sore throat, loss of smell or taste; Lower=shortness of breath with exertion, shortness of breath at rest, chest tightness, wheezing; Gastrointestinal=nausea, abdominal pain, diarrhea

**Duration of each symptom**

Table 3 describes the median days and 95% confidence interval for each symptom obtained from Kaplan-Meier survival curves, censoring symptoms if present at the final VOMC phone call. When present, cough had the longest duration with 17 days (95% confidence interval 15 to 21), followed by loss of smell or taste with 14 days (12 to 17) and sinus congestion with 13 days (11 to 15). Shortness of breath with exertion, when present, lasted 12 days (10 to 16).

Table 3 Median duration of symptoms from Kaplan-Meier curves for all patients*

| Symptom | Number patients with symptom | Median duration in days (95% CI) |
|---|---|---|
| Cough | 276 | 17 (15-21) |
| Loss of smell or taste | 232 | 14 (12-17) |
| Congestion | 244 | 13 (11-15) |
| SOB with exertion | 188 | 12 (10-16) |
| Body aches | 233 | 9 (8-10) |
| Chest tightness | 149 | 9 (7-12) |
| Headache | 258 | 9 (7-11) |
| Joint pain | 137 | 9 (7-11) |
| Rash | 33 | 9 (6-17) |
| Sore throat | 140 | 7 (6-9) |
| Nausea | 124 | 7 (6-8) |
| Current fever | 144 | 7 (5-8) |
| Diarrhea | 168 | 6 (5-8) |
| Chills | 195 | 6 (5-7) |
| Wheezing | 70 | 6 (4-9) |
| Dizziness | 150 | 5 (4-7) |
| SOB at rest | 88 | 5 (3-6) |
| Abdominal pain | 100 | 4 (2-6) |
| Confusion | 20 | 2 (1-3) |

SOB=shortness of breath
*censoring symptoms if present at the final VOMC phone call

Patients reporting improving symptoms could be discharged from VOMC with symptoms present. The percentage of patients reporting resolution of each symptom is presented in table 4. The symptoms most frequently unresolved at the time of the final phone call were cough (115 of 276 patients with cough, 42%), loss of smell or taste (89 of 232, 38%), sinus congestion (89 of 244, 36%), and shortness of breath with exertion (65 of 188, 35%).

Table 4 Symptoms unresolved at last phone call

| Symptom | Total patients with symptom at any time | Number symptomatic at last phone call | Percent unresolved at last phone call |
|---|---|---|---|
| Cough | 276 | 115 | 42% |
| Loss of smell or taste | 232 | 89 | 38% |
| Congestion | 244 | 89 | 36% |
| SOB with exertion | 188 | 65 | 35% |
| Body aches | 233 | 52 | 22% |
| Joint pain | 137 | 30 | 22% |
| Headache | 258 | 56 | 22% |
| SOB at rest | 88 | 19 | 22% |
| Rash | 33 | 7 | 21% |
| Sore throat | 140 | 28 | 20% |
| Nausea | 124 | 23 | 19% |
| Chest tightness | 149 | 27 | 18% |
| Dizziness | 150 | 24 | 16% |
| Wheezing | 70 | 11 | 16% |
| Confusion | 20 | 3 | 15% |
| Diarrhea | 168 | 23 | 14% |
| Current fever | 144 | 18 | 13% |
| Abdominal pain | 100 | 10 | 10% |
| Chills | 195 | 19 | 10% |

SOB=shortness of breath

**Symptom duration predicted by covariates**

Table 5 presents the results of the final AFT models with log-logistic distribution fitted individually for each symptom. The AFT duration multiplier is the factor by which the survival time is multiplied for that group compared to the reference group. For example,

obesity was the only significant predictor of joint pain duration with 1.74 (95% CI 1.09-2.76) fold longer duration, which is 74% (95% CI 9-176%) longer symptoms than those without obesity. Asthma was the only significant predictor for wheezing, increasing duration by 166% (95% CI 39-408%). Asthma and black race were both predictors of duration for SOB at rest, with asthma increasing SOB duration by 97% (95% CI 20-224%) and black race by 178% (63-407%). Diarrhea is more complex. Patients with moderate initial symptom severity had 72% longer (95% CI 24-138%) duration of diarrhea than those with mild initial symptom severity, while blacks had a 44% (95% CI -63 to -16%) shorter duration of diarrhea. Initial symptom severity (from VOMC intake visit) was a significant predictor for over half of our symptoms: body aches, chest tightness, chills, congestion, cough, diarrhea, dizziness, fever, headache, nausea, SOB with exertion, and sore throat (table 5). Moderate initial symptom severity increased symptom duration by an average of 63%. Severe initial symptom severity increased symptom duration by an average of 260% compared to those with mild initial symptom severity. The residual plots to analyze goodness of fit for each symptom's model are in supplement figure 2.

Table 5 Covariates affecting duration of symptoms derived from Accelerated Failure Time model with each symptom modeled separately

| Symptom | Covariate | Duration multiplier (95% CI) | p value |
|---|---|---|---|
| Abdominal pain | Immune suppression | 7.48 (3.26-17.18) | <0.001 |
| Body aches | Mild initial symptom severity* | reference | |
| | Moderate initial symptom severity | 1.87 (1.44-2.42) | <0.001 |
| | Severe initial symptom severity | 4.01 (1.66-9.68) | 0.002 |
| Chest tightness | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.36 (0.96-1.93) | 0.083 |
| | Severe initial symptom severity | 4.26 (1.68-10.78) | 0.002 |
| Chills | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.57 (1.21-2.03) | 0.001 |

| | | | |
|---|---|---|---|
| | Severe initial symptom severity | 2.75 (1.28-5.90) | 0.009 |
| Confusion | Race=White | reference | |
| | Race=Black | 1.65 (1.03-2.63) | 0.036 |
| | Race=Other | 7.44 (3.98-13.92) | <0.001 |
| Congestion | Female | 1.57 (1.12-2.20) | 0.009 |
| | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.66 (1.20-2.31) | 0.002 |
| | Severe initial symptom severity | 1.97 (0.59-6.57) | 0.27 |
| Cough | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.52 (1.15-1.99) | 0.003 |
| | Severe initial symptom severity | 3.46 (1.25-9.58) | 0.017 |
| Diarrhea | Race=White | reference | |
| | Race=Black | 0.56 (0.37-0.84) | 0.005 |
| | Race=Other | 0.61 (0.39-0.96) | 0.033 |
| | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.72 (1.24-2.38) | 0.001 |
| | Severe initial symptom severity | 3.41 (0.91-12.74) | 0.068 |
| Dizziness | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.79 (1.24-2.58) | 0.002 |
| | Severe initial symptom severity | 6.09 (1.80-20.54) | 0.004 |
| Fever | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.31 (0.92-1.87) | 0.132 |
| | Severe initial symptom severity | 4.76 (1.51-15.07) | 0.008 |
| | Immune suppression | 1.97 (1.01-3.85) | 0.048 |
| Headache | Female | 1.34 (1.01-1.79) | 0.043 |
| | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 2.10 (1.58-2.78) | <0.001 |
| | Severe initial symptom severity | 1.91 (0.74-4.98) | 0.184 |
| Joint pain | Obesity | 1.74 (1.09-2.76) | 0.019 |
| Loss of smell or taste | Female | 1.63 (1.24-2.13) | <0.001 |
| | Immune suppression | 3.06 (1.48-6.34) | 0.003 |
| Nausea | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.73 (1.15-2.61) | 0.009 |
| | Severe initial symptom severity | 2.76 (0.73-10.42) | 0.135 |
| SOB at rest | Race=White | reference | |
| | Race=Black | 2.87 (1.63-5.07) | <0.001 |
| | Race=Other | 1.50 (0.79-2.85) | 0.219 |
| | Asthma | 1.97 (1.20-3.24) | 0.007 |
| SOB with exertion | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.71 (1.16-2.52) | 0.006 |
| | Severe initial symptom severity | 1202794.22 (0.00-Inf) | 0.995 |

| | | | |
|---|---|---|---|
| Sore throat | Mild initial symptom severity | reference | |
| | Moderate initial symptom severity | 1.25 (0.83-1.88) | 0.279 |
| | Severe initial symptom severity | 4.22 (1.70-10.47) | 0.002 |
| Wheezing | Asthma | 2.66 (1.39-5.08) | 0.003 |

SOB=shortness of breath

*Initial symptom severity is the symptom severity as assessed by the provider at VOMC intake visit (see Box 1) or patient reported severity if provider-assessed severity not available.

## DISCUSSION

### Principal findings

Whereas other studies have looked at cross sectional analysis of covid-19 symptoms, our study describes the longitudinal symptom course over the acute illness period for a telemedicine cohort, including the duration of reporting for each symptom and predictors of symptom duration.

We found that symptom onset starts with upper respiratory and systemic symptoms followed by lower respiratory and GI symptoms. This is consistent with the fact that infected individuals produce large quantities of virus in the upper respiratory tract during the prodromal period.[23] An important observation in this study is that initial symptom severity (at intake visit after test result) was a predictor for the symptom profile over time. Initial symptom severity predicts duration for the majority of symptoms, with significant associations for upper and lower respiratory symptoms as well as non-respiratory symptoms (including body aches, dizziness, chills, fever, headache, nausea and diarrhea). Notable exceptions were joint pain and wheezing whose only predictors of symptom duration were the underlying risk factors of obesity and asthma, respectively. While these associations make sense clinically, an explanation for

immunosuppression leading to longer duration of specific symptoms (abdominal pain and loss of smell or taste) is less intuitive. To decrease the chance of finding false positives, we fit models only for covariates that were significant predictors of overall symptom duration with symptoms analyzed as strata, but some of the findings in the final models may be spurious. Nonetheless, the majority are very significant ($p<0.01$) along with clinically significant changes in duration.

**Comparison with other studies**

Initial symptoms reported are similar to previous studies of mild covid-19 and non-hospitalized subsets.[12,15] It differs from the overall reported literature, summarized in a systematic review of 148 studies.[14] Notably, fever was less common (n=121, 36%) compared with 78% in the systematic review, while other symptoms are more common, for example: headache (65% vs 13%), body aches (64% vs 17%), hyposmia (55% vs 25%). The higher frequency of multiple symptoms may be due to our systematic approach to symptom inquiry. Rate of fever may be underreported due to template wording “current fever” but also may be less frequent in this cohort as increased testing availability has expanded the symptom profile of “mild covid-19” patients eligible for testing (Box 1).

We find that the visual course of illness and predictors of symptom duration have not been well described and this is an important contribution of this analysis. Narrative reviews have noted symptom progression similar to our report[24] and the visual course

reported here in heat map form illustrates the development of respiratory symptoms during and after the first week of illness among patients never requiring hospitalization for covid-19. One longitudinal study of the first 10 days of illness included a follow-up call (day 30-45), reporting similar initial symptom profile (reporting loss of smell or taste, cough, fatigue and headache more common than fever) and persistent symptoms profile including loss of smell or taste, dyspnea, cough, and headache.[18] Notably, the investigators found fatigue (not captured in our study) was prominent at acute and follow-up calls.

In our experience, many patients present for evaluation of non-resolving symptoms in the weeks that follow acute covid-19.[21] Reports have noted long duration of medical leave among persons with covid-19, for example first responders in New York (leave duration mean 25.3 days, SD=13.2).[25] We are able to differentiate the likelihood of prolonged symptoms in our cohort using mild and moderate initial symptom severity, which may aid in clinical counseling and anticipation of symptom recovery times. Given reports of delayed recovery of symptoms after hospitalization,[26] and in outpatients [19] the differentiation by symptom severity in outpatients is plausible.

Comparisons to reports of the severe acute respiratory syndrome (SARS) in 2003 and the Middle East respiratory syndrome (MERS) are limited as mild cases of these diseases were uncommon and most patients with SARS and MERS required hospital admission (requiring intensive care in >20% of SARS cases and >50% of MERS cases).[27, 28] The sequence of symptoms we describe for covid-19 is similar to descriptions of SARS, with initial presentation of systemic symptoms and cough,

followed by lower respiratory symptoms and gastrointestinal manifestations.[27] Notable differences include that fever is universal in reports of SARS (99.9%) and upper respiratory symptoms are less common than with covid-19 (e.g. rhinorrhea, sore throat both <20%). Patients with MERS also more frequently have fever and dyspnea, with lower rates of upper respiratory symptoms.[28] Gastrointestinal symptoms appear at similar rates (20-30%) in SARS and MERS, despite the overall higher severity of respiratory disease.

**Strengths and limitations of study**

Our data on the course of symptoms in outpatients is robust due to the structure of the VOMC, which was staffed to meet the anticipated "surge" of patients in March-May 2020 and therefore had skilled providers contacting patients and completing full note templates regularly through the course of acute illness. Exclusion criteria was minimal and primarily in place to improve accuracy of symptom recollection. Missing clinical data were minimal (e.g. low risk patients contacted every 48 hours instead of 24 hours), allowing for standard approach to imputation.

The primary limitation of this study is that it represents a single-center cohort of patients early in the SARS-CoV-2 pandemic. Testing criteria favored the inclusion of working-age individuals in the cohort. We have limited numbers of patients with comorbidities and cannot therefore draw conclusions about the duration of symptoms related to specific conditions (e.g. chronic obstructive pulmonary disease). Furthermore, we note

that asymptomatic or mildly symptomatic cases would be less likely to qualify for testing at the time of this study (see criteria in Box 1) and may have been less likely, even if tested, to accept a referral to VOMC (we do not have data on reasons for declined referrals). Because of the relatively small size of the cohort, we also have small numbers of less common symptoms (e.g. confusion and rash).

Another limitation to the VOMC cohort data is the time delay to the VOMC intake visit. Our usual care requires a positive SARS-CoV-2 test prior to VOMC enrollment, and delays in the testing process or results notification could attenuate patient recall of initial symptoms. It is also possible that delays would reduce the intake of patients with severe symptoms (as they escalate to admission) as well as mild symptoms (as they resolve). To reduce the effects of testing delays on our study, we limited the study to patients within 10 days of symptom onset and used chart review to verify symptoms reported in the testing process.

Discharge timing in the VOMC was a limitation for our follow-up data: the VOMC discharge criteria mirrored the CDC terminology of symptom "improvement," but not resolution. The percent of patients still symptomatic at the last phone call varied among symptoms (table 4). We find in other work (unpublished data) that minor residual symptoms are common after VOMC discharge (reported in 55 of 158, 34.8%, of patients contacted a mean of 37.9 days after discharge) and that few (n=7, 4.4%) have symptoms requiring medical follow-up (e.g. by a primary care physician or

specialist).[29] These residual symptoms are not captured in the heat map data after their final VOMC call.

"Long covid" has now been described as symptoms persisting beyond the acute illness [30], including fatigue, palpitations, "brain fog" and other symptoms that were not known in March 2020. We have identified these symptoms in individual cases within the VOMC cohort who received prolonged care [19] but did not capture these specific symptoms during the acute care described in this study.

## CONCLUSION

Overall, we find that the symptom course of outpatients with covid-19 follows a pattern described in early observations with a typical illness course progressing from early symptoms (systemic, upper respiratory, and cough) to lower respiratory and gastrointestinal symptoms. We confirm that symptoms of altered smell or taste and headache are common in outpatients. Prolonged symptoms are common and the severity of symptoms in the acute phase of illness is the most significant predictor of disease duration.

## MANUSCRIPT INFORMATION

### Ethics

The study was approved by the Emory University Institutional Review Board (STUDY00000766), which granted both a waiver of informed consent and a waiver of the Health Information Portability and Privacy Act as the study posed no more than minimal risk.

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**Data Sharing Statement**: Deidentified data are available for sharing upon reasonable request to David Tong (ORCID 0000-0001-9761-6124). Data include patient demographics and comorbidities as well as symptom dates for all participants.

**Dissemination declaration**: We plan to disseminate our results publicly but it would not be feasible to reach discharged patients with study results and therefore we do not plan to contact study participants for dissemination.

**Conflict of Interest Disclosures**: All authors have completed the Unified Competing Interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work. Dr. G. O'Keefe served on an advisory board of Eyepoint Pharmaceuticals in 2019. It is unrelated to the current work.

**Author Contributions**:

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. David Tong had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

*Transparency statement*: David Tong attests that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

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## FIGURES

**Figure 1: Heatmap of incidence of individual symptoms by illness day**

Figure 1a: All patients, n=304 (% patients having symptom each day of covid-19 disease)

Figure 1b: Mild provider assessed symptom severity n=209

Figure 1c: Moderate provider assessed symptom severity n=91

| Legend (Percent of patients experiencing a symptom each day of COVID disease) | 0 | 20 | 40 | 60 | 80 | 100 |
|---|---|---|---|---|---|---|

All patients n=304

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| current fever | 22 | 22 | 21 | 20 | 18 | 18 | 16 | 14 | 11 | 8 | 10 | 9 | 5 | 3 | 2 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| chills | 27 | 34 | 35 | 34 | 31 | 29 | 26 | 19 | 18 | 12 | 10 | 9 | 6 | 5 | 5 | 4 | 3 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 |
| body aches | 37 | 43 | 45 | 46 | 42 | 37 | 35 | 34 | 32 | 26 | 23 | 21 | 19 | 16 | 14 | 11 | 9 | 7 | 8 | 7 | 7 | 7 | 6 | 7 | 6 | 6 | 5 | 4 | 4 | 4 |
| dizziness when standing | 5 | 11 | 12 | 15 | 15 | 16 | 14 | 15 | 15 | 14 | 13 | 11 | 10 | 10 | 7 | 5 | 6 | 5 | 3 | 3 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 0 | 1 | 0 |
| confusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| headache | 37 | 44 | 45 | 43 | 42 | 38 | 35 | 33 | 29 | 27 | 25 | 23 | 20 | 19 | 17 | 14 | 12 | 11 | 10 | 10 | 8 | 8 | 9 | 8 | 5 | 7 | 6 | 4 | 4 | 2 |
| loss of smell or taste | 22 | 30 | 37 | 42 | 48 | 50 | 50 | 50 | 48 | 43 | 41 | 33 | 29 | 27 | 25 | 18 | 20 | 16 | 13 | 12 | 10 | 9 | 8 | 8 | 7 | 7 | 5 | 4 | 3 | 2 |
| sinus congestion | 32 | 37 | 43 | 45 | 46 | 44 | 45 | 42 | 40 | 38 | 37 | 32 | 29 | 25 | 25 | 21 | 21 | 19 | 16 | 12 | 12 | 11 | 8 | 8 | 7 | 6 | 5 | 4 | 4 | 3 |
| sore throat | 21 | 24 | 23 | 22 | 20 | 17 | 16 | 14 | 13 | 10 | 10 | 7 | 7 | 7 | 7 | 6 | 6 | 6 | 6 | 3 | 3 | 3 | 2 | 3 | 3 | 2 | 1 | 2 | 1 | 1 |
| cough | 46 | 53 | 55 | 57 | 60 | 57 | 56 | 56 | 56 | 52 | 47 | 41 | 39 | 36 | 34 | 30 | 30 | 25 | 21 | 20 | 18 | 18 | 14 | 14 | 12 | 10 | 8 | 7 | 7 | 5 |
| chest tightness | 11 | 15 | 18 | 21 | 22 | 23 | 25 | 23 | 22 | 20 | 19 | 18 | 14 | 12 | 10 | 10 | 9 | 7 | 5 | 4 | 5 | 4 | 4 | 3 | 3 | 4 | 3 | 2 | 3 | 2 |
| shortness of breath at rest | 4 | 4 | 5 | 7 | 7 | 7 | 7 | 7 | 7 | 5 | 5 | 5 | 3 | 3 | 3 | 2 | 1 | 2 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | 0 | 0 |
| shortness of breath with exertion | 13 | 17 | 20 | 21 | 23 | 26 | 29 | 30 | 30 | 27 | 25 | 25 | 22 | 22 | 20 | 20 | 16 | 14 | 13 | 13 | 11 | 10 | 9 | 8 | 7 | 8 | 8 | 5 | 6 | 3 |
| wheezing | 3 | 4 | 5 | 6 | 6 | 7 | 7 | 6 | 7 | 6 | 5 | 4 | 2 | 1 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 |
| abdominal pain | 3 | 4 | 6 | 7 | 10 | 10 | 7 | 7 | 7 | 7 | 5 | 3 | 2 | 3 | 3 | 2 | 2 | 1 | 1 | 0 | 2 | 1 | 2 | 1 | 0 | 1 | 0 | 0 | 0 | 1 |
| nausea | 6 | 7 | 8 | 10 | 12 | 13 | 13 | 13 | 14 | 12 | 11 | 9 | 7 | 8 | 7 | 6 | 3 | 3 | 3 | 2 | 3 | 3 | 3 | 2 | 1 | 1 | 1 | 1 | 0 | 0 |
| diarrhea | 12 | 15 | 15 | 18 | 20 | 21 | 20 | 19 | 16 | 15 | 13 | 12 | 9 | 10 | 10 | 7 | 6 | 5 | 4 | 4 | 4 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 0 | 0 |
| joint pain | 9 | 13 | 15 | 17 | 18 | 18 | 17 | 14 | 14 | 12 | 13 | 14 | 12 | 11 | 10 | 8 | 7 | 7 | 6 | 5 | 4 | 5 | 4 | 4 | 3 | 3 | 3 | 3 | 3 | 2 |
| rash | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 |

Mild initial symptoms = 209

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| current fever | 19 | 19 | 17 | 17 | 14 | 14 | 11 | 11 | 8 | 6 | 7 | 5 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| chills | 26 | 30 | 29 | 27 | 22 | 20 | 16 | 12 | 10 | 6 | 5 | 4 | 3 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| body aches | 34 | 38 | 38 | 36 | 31 | 26 | 23 | 22 | 20 | 18 | 16 | 13 | 13 | 9 | 7 | 6 | 4 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 2 | 2 | 2 | 1 | 1 | 1 |
| dizziness when standing | 2 | 7 | 8 | 11 | 10 | 10 | 6 | 7 | 8 | 9 | 8 | 6 | 6 | 5 | 4 | 2 | 2 | 1 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| confusion | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| headache | 33 | 40 | 39 | 36 | 35 | 32 | 29 | 25 | 21 | 20 | 20 | 14 | 12 | 13 | 11 | 10 | 7 | 6 | 7 | 6 | 5 | 5 | 6 | 4 | 3 | 4 | 4 | 2 | 2 | 1 |
| loss of smell or taste | 21 | 27 | 34 | 38 | 44 | 46 | 45 | 44 | 43 | 38 | 36 | 27 | 24 | 23 | 21 | 14 | 15 | 11 | 9 | 8 | 7 | 6 | 5 | 5 | 4 | 5 | 3 | 1 | 1 | 0 |
| sinus congestion | 31 | 36 | 43 | 45 | 44 | 43 | 40 | 37 | 34 | 32 | 33 | 25 | 24 | 21 | 18 | 17 | 14 | 13 | 9 | 7 | 6 | 6 | 5 | 4 | 4 | 2 | 2 | 1 | 1 | 1 |
| sore throat | 19 | 24 | 22 | 22 | 19 | 15 | 12 | 11 | 10 | 9 | 10 | 6 | 5 | 4 | 4 | 4 | 5 | 5 | 6 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| cough | 40 | 47 | 48 | 49 | 52 | 50 | 47 | 46 | 47 | 43 | 38 | 31 | 29 | 27 | 24 | 22 | 21 | 18 | 13 | 11 | 11 | 11 | 9 | 7 | 6 | 5 | 4 | 1 | 3 | 1 |
| chest tightness | 9 | 11 | 12 | 14 | 17 | 17 | 16 | 15 | 14 | 13 | 14 | 13 | 10 | 7 | 7 | 7 | 6 | 6 | 4 | 3 | 3 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| shortness of breath at rest | 3 | 3 | 2 | 3 | 3 | 4 | 3 | 5 | 4 | 3 | 3 | 4 | 2 | 3 | 2 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| shortness of breath with exertion | 5 | 8 | 10 | 11 | 12 | 15 | 17 | 20 | 18 | 16 | 15 | 14 | 13 | 13 | 11 | 13 | 9 | 8 | 8 | 7 | 6 | 5 | 5 | 4 | 3 | 3 | 3 | 1 | 2 | 1 |
| wheezing | 2 | 2 | 2 | 3 | 4 | 5 | 4 | 3 | 4 | 4 | 4 | 4 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| abdominal pain | 3 | 1 | 3 | 5 | 7 | 7 | 4 | 5 | 4 | 5 | 3 | 2 | 1 | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nausea | 3 | 4 | 5 | 8 | 9 | 10 | 9 | 9 | 11 | 9 | 9 | 5 | 3 | 5 | 5 | 3 | 1 | 1 | 1 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| diarrhea | 10 | 11 | 10 | 13 | 14 | 15 | 13 | 14 | 10 | 11 | 8 | 7 | 6 | 8 | 7 | 3 | 2 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| joint pain | 7 | 9 | 10 | 11 | 12 | 11 | 8 | 7 | 6 | 6 | 6 | 8 | 7 | 7 | 6 | 5 | 3 | 3 | 2 | 3 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 0 |
| rash | 0 | 1 | 0 | 1 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 0 | 0 |

Moderate initial symptoms n = 91

| Symptom | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| current fever | 27 | 29 | 28 | 25 | 25 | 26 | 26 | 17 | 15 | 10 | 15 | 16 | 8 | 6 | 4 | 3 | 2 | 3 | 3 | 2 | 2 | 1 | 1 | 1 | 1 | 0 | 2 | 1 | 2 | 1 |
| chills | 28 | 41 | 46 | 48 | 49 | 48 | 49 | 31 | 34 | 24 | 19 | 16 | 12 | 7 | 7 | 7 | 5 | 2 | 2 | 2 | 3 | 2 | 5 | 5 | 3 | 3 | 3 | 4 | 5 | 1 |
| body aches | 41 | 53 | 59 | 67 | 67 | 59 | 61 | 58 | 58 | 41 | 37 | 36 | 28 | 28 | 27 | 20 | 19 | 13 | 16 | 14 | 16 | 13 | 12 | 12 | 14 | 13 | 10 | 9 | 9 | 8 |
| dizziness when standing | 12 | 19 | 21 | 25 | 26 | 27 | 30 | 31 | 31 | 26 | 25 | 24 | 19 | 18 | 13 | 9 | 14 | 10 | 8 | 8 | 5 | 3 | 5 | 3 | 5 | 2 | 1 | 1 | 1 | 1 |
| confusion | 1 | 1 | 0 | 0 | 0 | 0 | 3 | 2 | 1 | 0 | 0 | 0 | 2 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| headache | 43 | 50 | 56 | 58 | 56 | 52 | 50 | 50 | 49 | 42 | 37 | 42 | 35 | 31 | 32 | 23 | 23 | 21 | 17 | 19 | 16 | 15 | 14 | 16 | 8 | 13 | 9 | 9 | 8 | 4 |
| loss of smell or taste | 21 | 36 | 41 | 50 | 54 | 57 | 60 | 62 | 59 | 50 | 50 | 45 | 39 | 32 | 30 | 25 | 26 | 26 | 18 | 19 | 16 | 16 | 14 | 14 | 10 | 12 | 9 | 9 | 6 | 5 |
| sinus congestion | 35 | 41 | 43 | 45 | 49 | 46 | 54 | 51 | 53 | 50 | 45 | 47 | 39 | 36 | 39 | 29 | 36 | 31 | 30 | 24 | 26 | 23 | 15 | 18 | 13 | 16 | 13 | 10 | 10 | 8 |
| sore throat | 23 | 24 | 23 | 21 | 19 | 19 | 20 | 17 | 18 | 10 | 9 | 8 | 8 | 14 | 13 | 9 | 6 | 7 | 5 | 3 | 4 | 6 | 4 | 9 | 7 | 7 | 4 | 5 | 3 | 2 |
| cough | 58 | 67 | 72 | 74 | 75 | 73 | 74 | 76 | 76 | 71 | 64 | 62 | 61 | 54 | 52 | 47 | 48 | 39 | 37 | 38 | 31 | 31 | 23 | 27 | 20 | 19 | 16 | 16 | 13 | 9 |
| chest tightness | 14 | 21 | 28 | 31 | 30 | 34 | 42 | 39 | 37 | 30 | 26 | 27 | 20 | 21 | 16 | 13 | 10 | 7 | 7 | 6 | 7 | 8 | 7 | 8 | 6 | 9 | 8 | 6 | 8 | 4 |
| shortness of breath at rest | 8 | 8 | 10 | 15 | 15 | 14 | 16 | 9 | 13 | 7 | 8 | 5 | 3 | 3 | 5 | 1 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 2 | 1 | 3 | 2 | 2 | 1 | 1 |
| shortness of breath with exertion | 27 | 35 | 39 | 42 | 43 | 49 | 53 | 50 | 56 | 50 | 45 | 45 | 39 | 38 | 39 | 31 | 29 | 25 | 21 | 24 | 19 | 18 | 15 | 15 | 12 | 17 | 14 | 12 | 9 | 5 |
| wheezing | 5 | 8 | 10 | 13 | 10 | 12 | 15 | 15 | 14 | 10 | 8 | 5 | 4 | 3 | 3 | 3 | 3 | 3 | 2 | 2 | 3 | 5 | 5 | 2 | 3 | 2 | 3 | 2 | 2 | 1 |
| abdominal pain | 4 | 9 | 13 | 12 | 17 | 15 | 13 | 12 | 14 | 12 | 10 | 6 | 4 | 6 | 7 | 6 | 5 | 4 | 5 | 1 | 5 | 5 | 6 | 5 | 2 | 4 | 2 | 2 | 0 | 3 |
| nausea | 13 | 13 | 15 | 14 | 17 | 19 | 24 | 23 | 21 | 19 | 17 | 17 | 14 | 14 | 12 | 12 | 7 | 7 | 6 | 6 | 7 | 6 | 7 | 7 | 4 | 5 | 4 | 3 | 2 | 2 |
| diarrhea | 17 | 25 | 28 | 28 | 31 | 36 | 35 | 31 | 31 | 26 | 25 | 24 | 18 | 15 | 18 | 16 | 14 | 15 | 12 | 10 | 9 | 6 | 6 | 5 | 5 | 3 | 4 | 3 | 1 | 0 |
| joint pain | 14 | 21 | 28 | 31 | 32 | 32 | 36 | 31 | 30 | 25 | 28 | 28 | 21 | 21 | 19 | 16 | 17 | 16 | 15 | 9 | 8 | 6 | 7 | 7 | 6 | 8 | 9 | 7 | 6 | 6 |
| rash | 3 | 3 | 3 | 3 | 3 | 2 | 4 | 3 | 3 | 2 | 3 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 1 |

Supplement

Table 1 Cox models with AIC (time interaction terms for time varying covariates)

| Symptom | Covariates | Hazard Ratio (95% CI) | p value | AIC |
|---|---|---|---|---|
| Abdominal Pain | Immune suppression | 0.26 (0.11-0.62) | 0.002 | 654.96 |
| Body aches | Female | 1.3 (0.71-2.38) | 0.392 | 1656.88 |
| | Mild initial symptom severity | reference | | |
| | Moderate initial symptom severity | 0.5 (0.36-0.68) | <0.001 | |
| | Severe initial symptom severity | 0.28 (0.09-0.9) | 0.033 | |
| | time*Female | 0.9 (0.84-0.96) | 0.001 | |
| Chest Tightness | Mild initial symptom severity | reference | | 996.36 |
| | Moderate initial symptom severity | 0.72 (0.49-1.04) | 0.076 | |
| | Severe initial symptom severity | 0.26 (0.08-0.85) | 0.025 | |
| Chills | Female | 0.72 (0.52-0.99) | 0.047 | 1522.9 |
| | Mild initial symptom severity | reference | | |
| | Moderate initial symptom severity | 0.57 (0.42-0.78) | 0.000 | |
| | Severe initial symptom severity | 0.36 (0.14-0.91) | 0.030 | |
| Confusion | No significant covariates | 0.73 (0.22-2.38) | 0.600 | 73.94 |
| Sinus Congestion | Female | 0.65 (0.46-0.9) | 0.011 | 1460.06 |
| | Mild initial symptom severity | reference | | |
| | Moderate initial symptom severity | 0.59 (0.42-0.83) | 0.003 | |
| | Severe initial symptom severity | 0.64 (0.16-2.6) | 0.531 | |
| Cough | Mild initial symptom severity | reference | | 1529.85 |
| | Moderate initial symptom severity | 0.64 (0.46-0.89) | 0.008 | |
| | Severe initial symptom severity | 0.24 (0.06-0.96) | 0.044 | |
| Diarrhea | Race=White | reference | | 1195.59 |
| | Race=Black | 1.66 (1.05-2.63) | 0.029 | |
| | Race=Other | 1.69 (1.03-2.78) | 0.038 | |
| | Mild initial symptom severity | reference | | |
| | Moderate initial symptom severity | 0.63 (0.44-0.89) | 0.008 | |
| | Severe initial symptom severity | 0.3 (0.07-1.24) | 0.096 | |
| Dizziness | Mild initial symptom severity | reference | | 1029.99 |
| | Moderate initial symptom severity | 0.6 (0.42-0.86) | 0.005 | |
| | Severe initial symptom severity | 0.24 (0.06-1) | 0.050 | |
| Current Fever | Mild initial symptom severity | reference | | 995.01 |
| | Moderate initial symptom severity | 0.74 (0.51-1.08) | 0.118 | |
| | Severe initial symptom severity | 0.16 (0.04-0.74) | 0.018 | |
| | Immune suppression | 0.4 (0.17-0.93) | 0.033 | |
| | Obesity | 0.63 (0.42-0.93) | 0.022 | |
| Headache | Female | 0.61 (0.45-0.83) | 0.002 | 1891.72 |
| | Mild initial symptom severity | reference | | |
| | Moderate initial symptom severity | 0.5 (0.37-0.68) | 0.000 | |
| | Severe initial symptom severity | 0.49 (0.16-1.56) | 0.231 | |
| Joint Pain | Obesity | 0.67 (0.44-1.01) | 0.059 | 880.52 |

| | | | | |
|---|---|---|---|---|
| Loss of smell or taste | Female | 0.52 (0.36-0.74) | <0.001 | 1296.92 |
| | Immune suppression | 0.25 (0.08-0.79) | 0.018 | |
| Nausea | Female | 0.56 (0.35-0.91) | 0.018 | 793.72 |
| Rash | No significant covariates | 0.36 (0.04-2.86) | 0.332 | |
| SOB with exertion | No significant covariates | 1.36 (0.55-3.33) | 0.502 | |
| SOB at rest | Race=White | reference | | 493.45 |
| | Race=Black | 0.38 (0.19-0.76) | 0.006 | |
| | Race=Other | 0.62 (0.3-1.29) | 0.203 | |
| Sore Throat | Mild initial symptom severity | reference | | 891.43 |
| | Moderate initial symptom severity | 0.88 (0.49-1.59) | 0.673 | |
| | Severe initial symptom severity | 0.04 (0-1.01) | 0.051 | |
| | time*Moderate initial symptom severity | 0.97 (0.92-1.02) | 0.253 | |
| | time*Severe initial symptom severity | 1.11 (0.97-1.27) | 0.144 | |
| Wheezing | Asthma | 0.37 (0.19-0.7) | 0.002 | 387.95 |

SOB=shortness of breath

Table 2 Univariate analysis of covariates predicting symptom duration with symptom analyzed as strata comparing accelerated time models (AFT) and Cox proportional hazards

| Covariate | AFT log logistic distribution p value | AFT log normal distribution p value | Cox PH p value |
|---|---|---|---|
| Female | <0.001 | <0.001 | <0.001 |
| Moderate initial symptom severity | <0.001 | <0.001 | <0.001 |
| Severe initial symptom severity | <0.001 | <0.001 | <0.001 |
| Race = Black | 0.612 | <0.844 | 0.137 |
| Race = Others | 0.21 | <0.223 | 0.578 |
| Age > 60 | 0.112 | 0.103 | 0.018 |
| Alcohol abuse | 0.339 | 0.340 | 0.059 |
| Asthma | <0.001 | <0.001 | <0.001 |
| Cancer | 0.227 | 0.324 | 0.306 |
| Pregnant | 0.065 | 0.056 | 0.39 |
| COPD | 0.306 | 0.156 | 0.104 |
| CAD | 0.215 | 0.372 | 0.264 |
| Diabetes | 0.412 | 0.423 | 0.213 |
| Drug abuse | 0.373 | 0.359 | 0.087 |
| Heart failure | 0.304 | 0.246 | 0.144 |
| Hypertension | 0.109 | 0.242 | 0.212 |
| Immune suppression | <0.001 | <0.001 | <0.001 |
| Lung disease | 0.165 | 0.394 | 0.152 |
| Obesity | <0.001 | <0.001 | 0.001 |
| Renal disease | 0.781 | 0.753 | 0.938 |

CAD=Coronary artery disease; COPD=Chronic obstructive pulmonary disease

Table 3 Aikake information criteria for different distributions in the accelerated failure time model before removing nonsignificant covariates

| Symptom | Log Normal | Log Logistic | Exponential | Weibull | Logistic | Gaussian | CoxPH |
|---|---|---|---|---|---|---|---|
| Abdominal Pain | 522.31 | 528.74 | 538.46 | 540.07 | 641.16 | 661.67 | 662.13 |
| Body Aches | 1271.56 | 1268.97 | 1297.72 | 1287.54 | 1433.33 | 1457.26 | 1668.71 |
| Chest Tightness | 869.11 | 871.32 | 873.9 | 868.28 | 935.01 | 941.97 | 1001.29 |
| Chills | 1047.42 | 1052.25 | 1070.01 | 1050.3 | 1150.68 | 1190 | 1529.56 |
| Confusion | 56.61 | 57.37 | 78.53 | 54.12 | 59.32 | 59.33 | 69.03 |
| Congestion | 1219.12 | 1217.91 | 1218.98 | 1217.15 | 1328.11 | 1331.83 | 1467.46 |
| Cough | 1355.72 | 1348.91 | 1361.19 | 1346.34 | 1424 | 1420.67 | 1537.54 |
| Diarrhea | 906.87 | 916 | 921.74 | 917.28 | 1009.03 | 1020.68 | 1202.37 |
| Dizziness | 779.7 | 787.85 | 792.09 | 792.42 | 899.24 | 910.85 | 1033.56 |
| Current Fever | 775.89 | 783.77 | 781.93 | 773.33 | 848.94 | 853.62 | 998.89 |
| Headache | 1423.19 | 1427.12 | 1435.94 | 1431.09 | 1581.8 | 1596.36 | 1899.1 |
| Joint Pain | 767.77 | 771.15 | 772.18 | 773.85 | 871.19 | 879.27 | 883.76 |
| Loss of smell or taste | 1127.54 | 1119.6 | 1147.22 | 1118.66 | 1181.16 | 1183.8 | 1301.67 |
| Nausea | 660.31 | 663.2 | 666.42 | 666.23 | 740.78 | 750.79 | 801.15 |
| Rash | 193.51 | 195.34 | 190.98 | 191.71 | 202.77 | 201.81 | 140.62 |
| SOB at rest | 393.58 | 397.14 | 406.33 | 405.56 | 479.09 | 496.32 | 493.19 |
| SOB with exertion | 957.25 | 959.16 | 959.53 | 960.89 | 1045.89 | 1050.46 | 1085.54 |
| Sore Throat | 758.05 | 760.69 | 767.72 | 767.27 | 855.31 | 874.14 | 899.92 |
| Wheezing | 373.17 | 375.35 | 374.05 | 374.66 | 435.96 | 444.06 | 395.88 |

SOB=shortness of breath

* Covariates were Gender, initial symptom severity, Race, Asthma, Immunosuppression and Obesity for all models

Table 4 Comparing final AFT models with log normal and log logistic distributions

| Symptom | Covariate | Log normal Duration Multiplier | p value | Log logistic Duration Multiplier | p value |
|---|---|---|---|---|---|
| Abdominal Pain | Immune suppression | 6.95 (2.91-16.57) | <0.001 | 7.48 (3.26-17.18) | <0.001 |
| Body Aches | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.90 (1.45-2.49) | <0.001 | 1.87 (1.44-2.42) | <0.001 |
| | Severe initial symptom severity | 3.40 (1.43-8.07) | 0.006 | 4.01 (1.66-9.68) | 0.002 |
| Chest Tightness | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.47 (1.03-2.08) | 0.032 | 1.36 (0.96-1.93) | 0.083 |
| | Severe initial symptom severity | 4.83 (1.65-14.11) | 0.004 | 4.26 (1.68-10.78) | 0.002 |
| Chills | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.54 (1.19-2.00) | 0.001 | 1.57 (1.21-2.03) | 0.001 |
| | Severe initial symptom severity | 2.71 (1.26-5.84) | 0.011 | 2.75 (1.28-5.90) | 0.009 |
| Confusion | Race=White | reference | | reference | |
| | Race=Black | 1.90 (1.15-3.15) | 0.013 | 1.65 (1.03-2.63) | 0.036 |
| | Race=Other | 6.48 (3.16-13.30) | <0.001 | 7.44 (3.98-13.92) | <0.001 |
| | Obesity | 0.65 (0.43-0.99) | 0.046 | Not in model | |

| | | | | | |
|---|---|---|---|---|---|
| Congestion | Female | 1.57 (1.11-2.22) | 0.011 | 1.57 (1.12-2.20) | 0.009 |
| | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.61 (1.15-2.27) | 0.006 | 1.66 (1.20-2.31) | 0.002 |
| | Severe initial symptom severity | 2.24 (0.54-9.28) | 0.265 | 1.97 (0.59-6.57) | 0.27 |
| Cough | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.49 (1.11-2.00) | 0.008 | 1.52 (1.15-1.99) | 0.003 |
| | Severe initial symptom severity | 4.07 (1.27-13.02) | 0.018 | 3.46 (1.25-9.58) | 0.017 |
| Diarrhea | Race=White | reference | | reference | |
| | Race=Black | 0.57 (0.38-0.85) | 0.006 | 0.56 (0.37-0.84) | 0.005 |
| | Race=Other | 0.62 (0.40-0.97) | 0.037 | 0.61 (0.39-0.96) | 0.033 |
| | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.69 (1.23-2.31) | 0.001 | 1.72 (1.24-2.38) | 0.001 |
| | Severe initial symptom severity | 3.41 (1.00-11.68) | 0.051 | 3.41 (0.91-12.74) | 0.068 |
| Dizziness | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.72 (1.21-2.44) | 0.002 | 1.79 (1.24-2.58) | 0.002 |
| | Severe initial symptom severity | 6.08 (1.53-24.13) | 0.01 | 6.09 (1.80-20.54) | 0.004 |
| Fever | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.19 (0.84-1.67) | 0.325 | 1.31 (0.92-1.87) | 0.132 |
| | Severe initial symptom severity | 4.41 (1.22-15.89) | 0.023 | 4.76 (1.51-15.07) | 0.008 |
| | Immune suppression | 2.18 (1.08-4.37) | 0.029 | 1.97 (1.01-3.85) | 0.048 |
| | Obesity | 1.44 (1.01-2.07) | 0.045 | Not in model | |
| Headache | Female | Not in model | | 1.34 (1.01-1.79) | 0.043 |
| | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 2.16 (1.62-2.88) | <0.001 | 2.10 (1.58-2.78) | <0.001 |
| | Severe initial symptom severity | 2.42 (0.93-6.31) | 0.071 | 1.91 (0.74-4.98) | 0.184 |
| Joint Pain | Obesity | 1.63 (1.04-2.57) | 0.034 | 1.74 (1.09-2.76) | 0.019 |
| Loss of smell or taste | Female | 1.69 (1.26-2.26) | <0.001 | 1.63 (1.24-2.13) | <0.001 |
| | Immune suppression | 3.42 (1.52-7.70) | 0.003 | 3.06 (1.48-6.34) | 0.003 |
| Nausea | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.64 (1.10-2.44) | 0.016 | 1.73 (1.15-2.61) | 0.009 |
| | Severe initial symptom severity | 2.46 (0.73-8.29) | 0.147 | 2.76 (0.73-10.42) | 0.135 |
| SOB at rest | Race=White | reference | | reference | |
| | Race=Black | 2.77 (1.57-4.88) | <0.001 | 2.87 (1.63-5.07) | <0.001 |
| | Race=Other | 1.51 (0.80-2.85) | 0.2 | 1.50 (0.79-2.85) | 0.219 |
| | Asthma | 1.91 (1.18-3.12) | 0.009 | 1.97 (1.20-3.24) | 0.007 |
| | Immune suppression | 4.17 (1.14-15.24) | 0.031 | Not in model | |
| SOB with exertion | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.76 (1.19-2.60) | 0.005 | 1.71 (1.16-2.52) | 0.006 |
| | Severe initial symptom severity | 3911.07 (0.00-Inf) | 0.99 | 1202794.22 (0.00-Inf) | 0.995 |
| Sore Throat | Mild initial symptom severity | reference | | reference | |
| | Moderate initial symptom severity | 1.22 (0.83-1.79) | 0.318 | 1.25 (0.83-1.88) | 0.279 |
| | Severe initial symptom severity | 4.24 (1.46-12.35) | 0.008 | 4.22 (1.70-10.47) | 0.002 |
| Wheezing | Asthma | 2.28 (1.25-4.15) | 0.007 | 2.66 (1.39-5.08) | 0.003 |

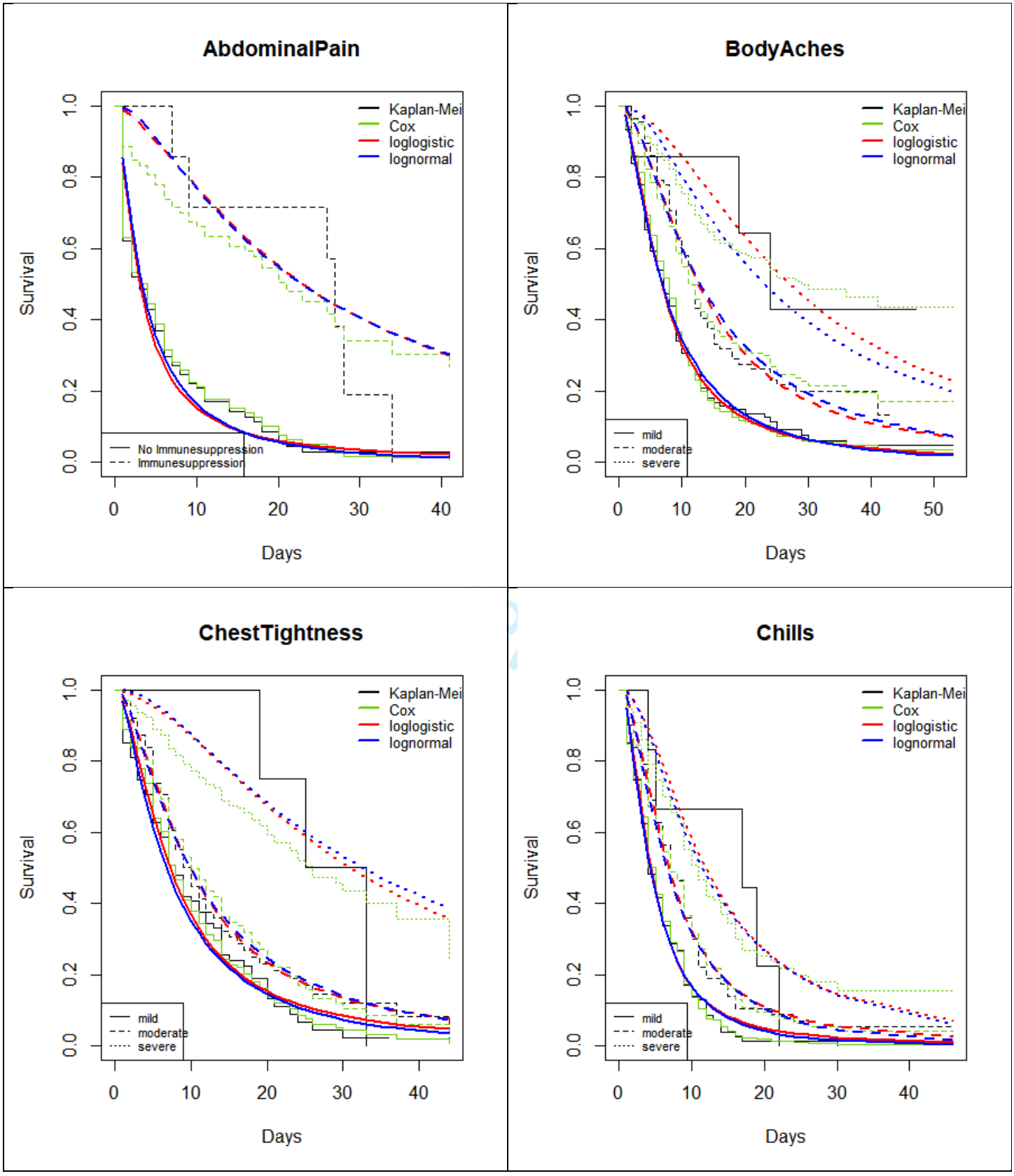
SOB=shortness of breath

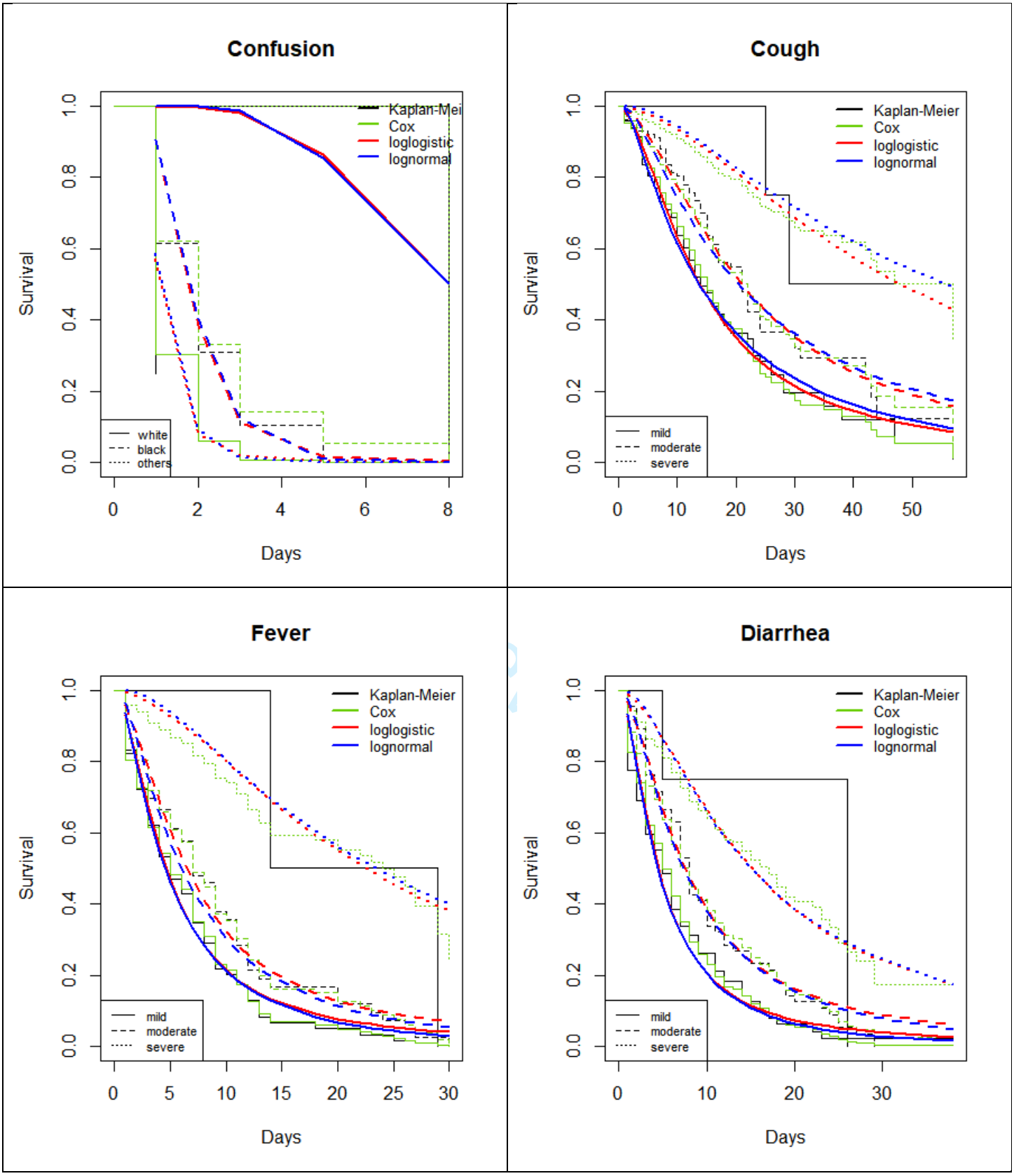
Table 5 AIC for AFT models for each symptoms similar comparing imputing provider assessed symptom severity with using related observation of self reported symptom severity

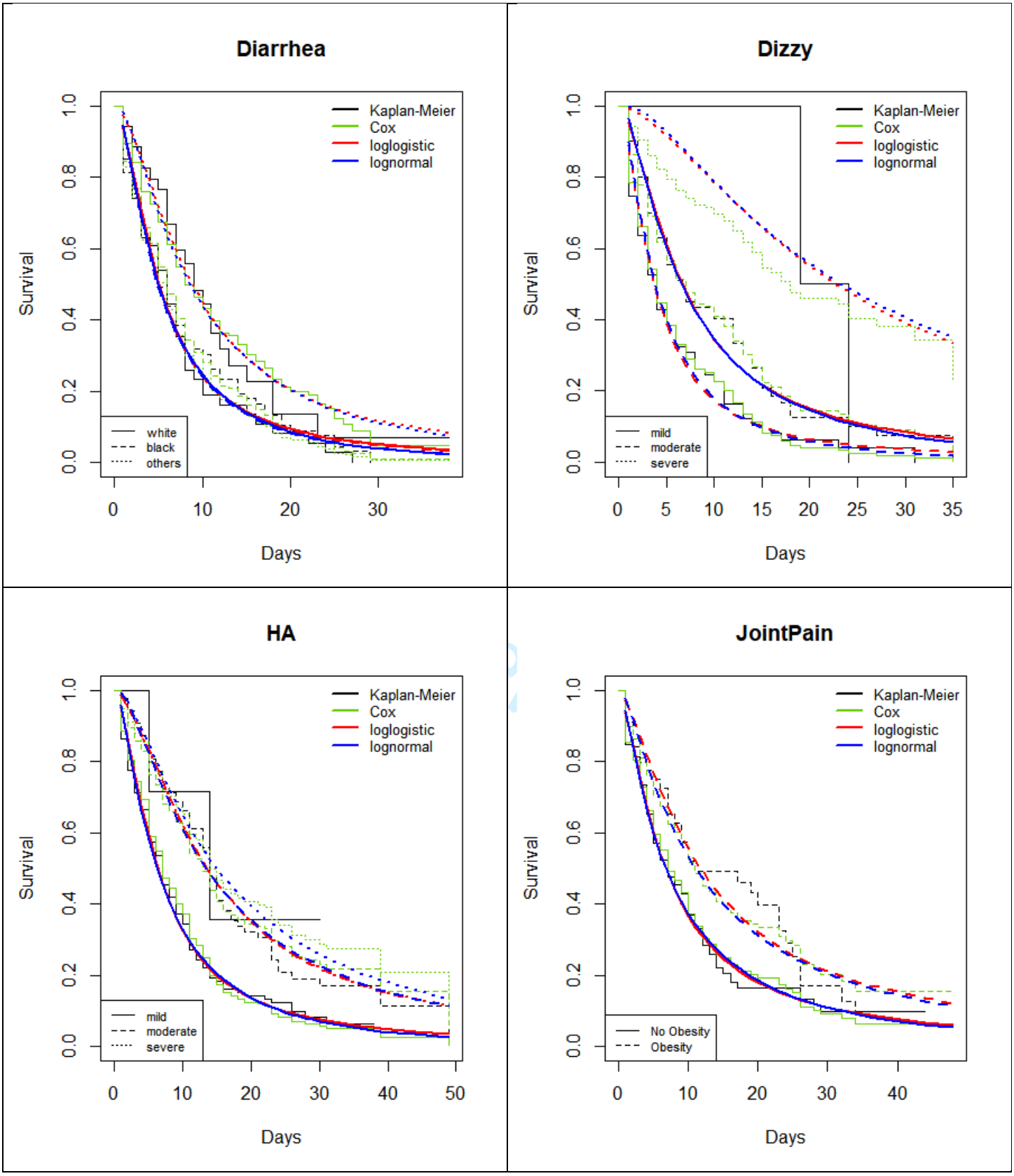
| Symptom | Using patient self reported symptom severity if provider assessed symptom severity missing (log-logistic distribution) | Imputed initial provider assessed symptom severity if provider assessed symptom severity missing (log-logistic distribution) |
|---|---|---|
| Abdominal Pain | 520.1 | 520.1 |
| Body Aches | 1267.75 | 1267.75 |
| Chest Tightness | 866.08 | 866.82 |
| Chills | 1044.26 | 1044.66 |
| Confusion | 53.45 | 53.45 |
| Congestion | 1209.54 | 1210.35 |
| Cough | 1342.34 | 1344.29 |
| Diarrhea | 909.39 | 909.37 |
| Dizzy | 781.09 | 782.33 |
| Fever | 778.75 | 778.75 |
| Headache | 1418.73 | 1419.43 |
| Joint Pain | 766.18 | 766.18 |
| Loss of smell or taste | 1113.56 | 1113.56 |
| Nausea | 657.75 | 657.53 |
| Rash | 185.65 | 185.65 |
| SOB at rest | 390.65 | 390.65 |
| SOB with exertion | 954.27 | 955.19 |
| Sore Throat | 757.25 | 757.25 |
| Wheezing | 368.78 | 368.78 |

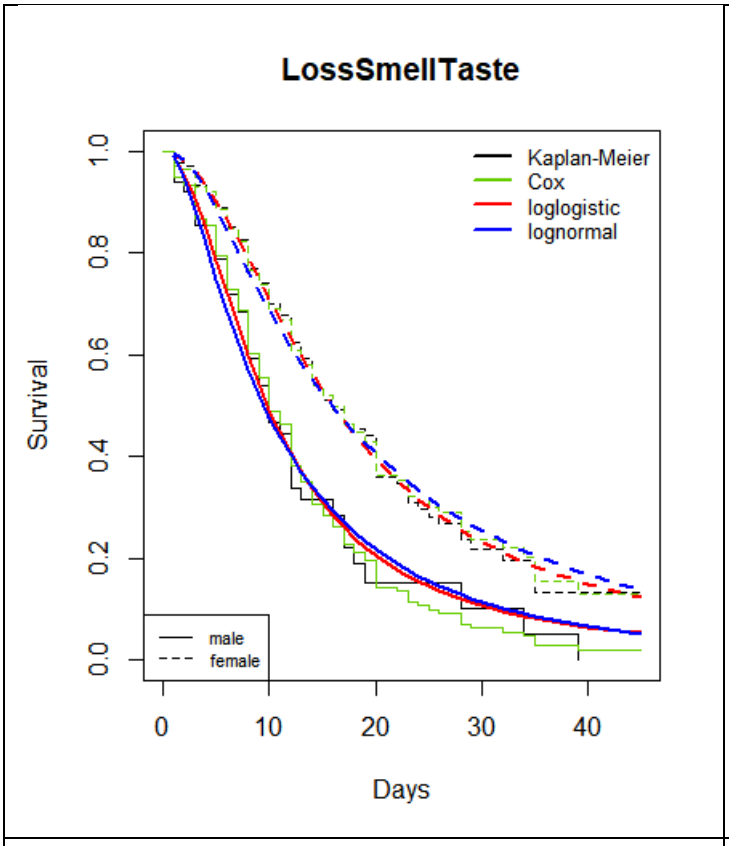
SOB=shortness of breath

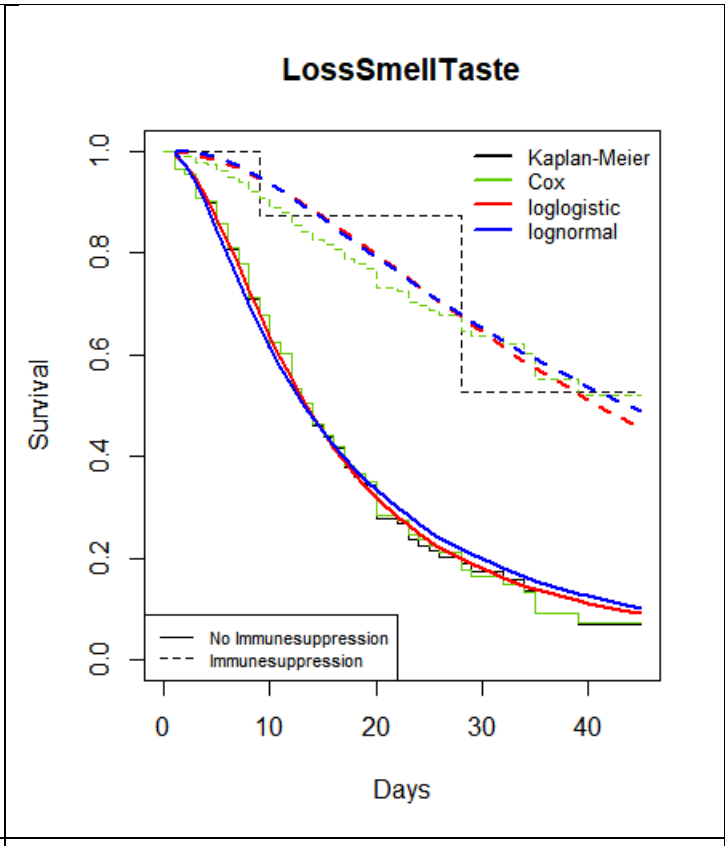
Figure 1 Survival curves for different models

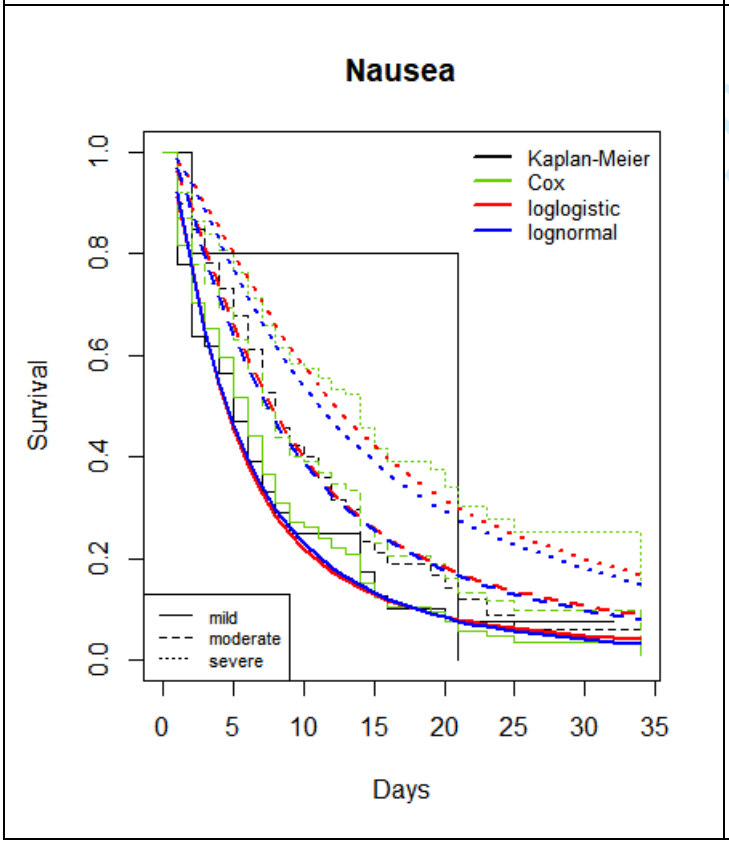


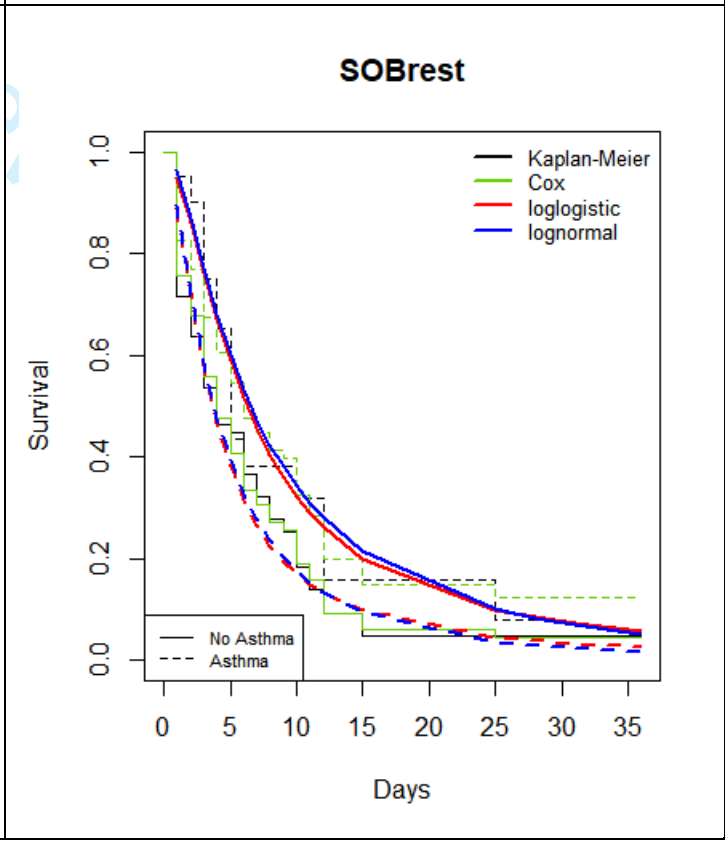

Confusion
Survival
Days
Kaplan-Mei
Cox
loglogistic
lognormal
white
black
others
Cough
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe
Fever
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe
Diarrhea
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe

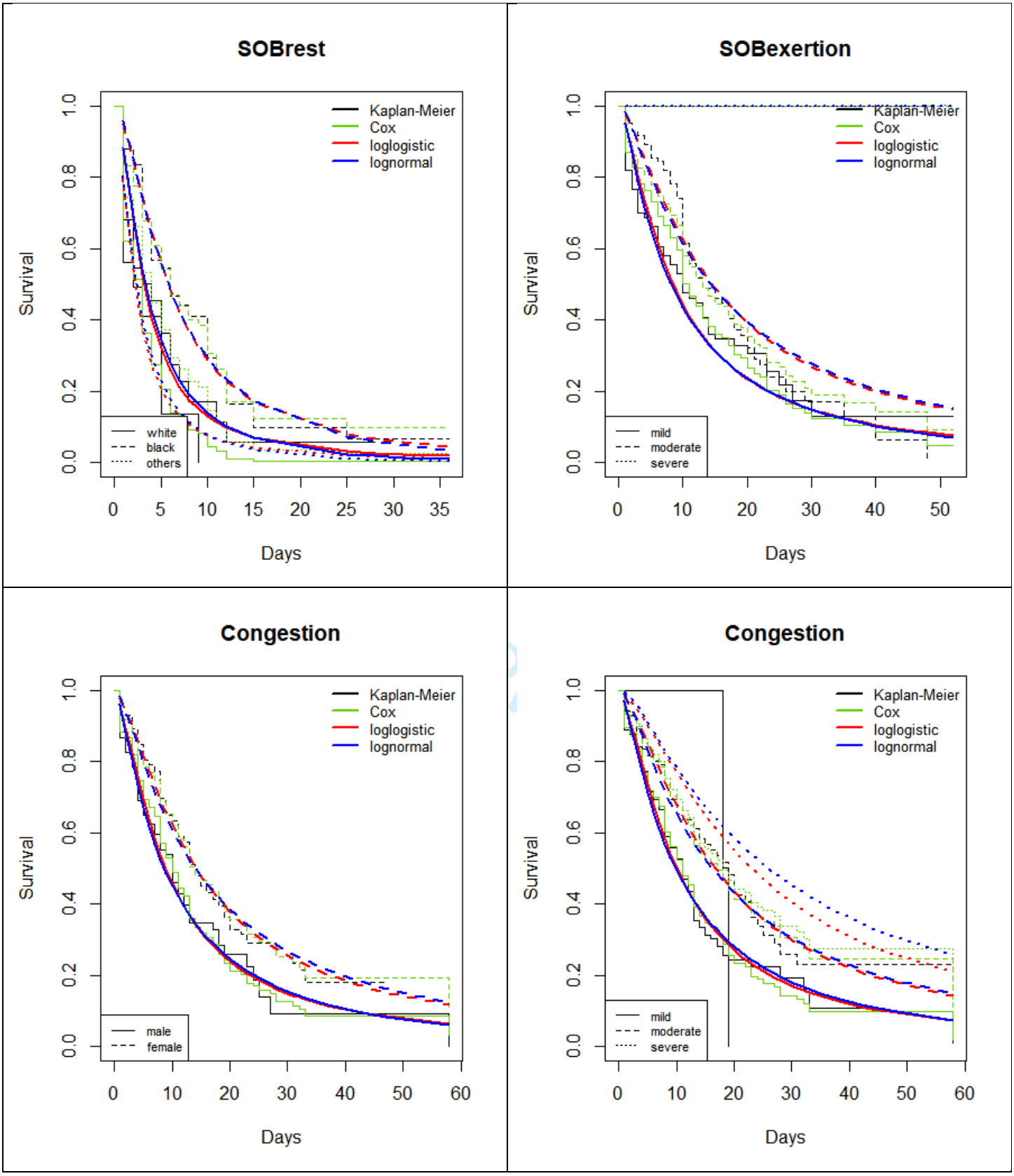

Diarrhea
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
white
black
others
Dizzy
mild
moderate
severe
HA
JointPain
No Obesity
Obesity

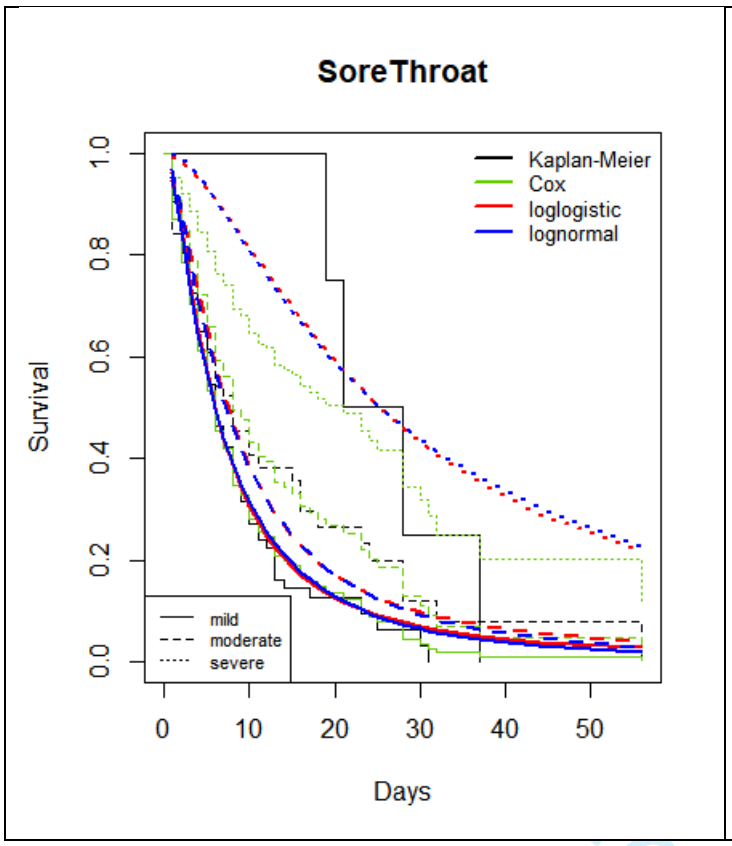

LossSmellTaste
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
male
female


LossSmellTaste
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
No Immunesuppression
Immunesuppression


Nausea
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe


SOBrest
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
No Asthma
Asthma


SOBrest
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
white
black
others
SOBexertion
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe
Congestion
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
male
female
Congestion
Survival
Days
Kaplan-Meier
Cox
loglogistic
lognormal
mild
moderate
severe



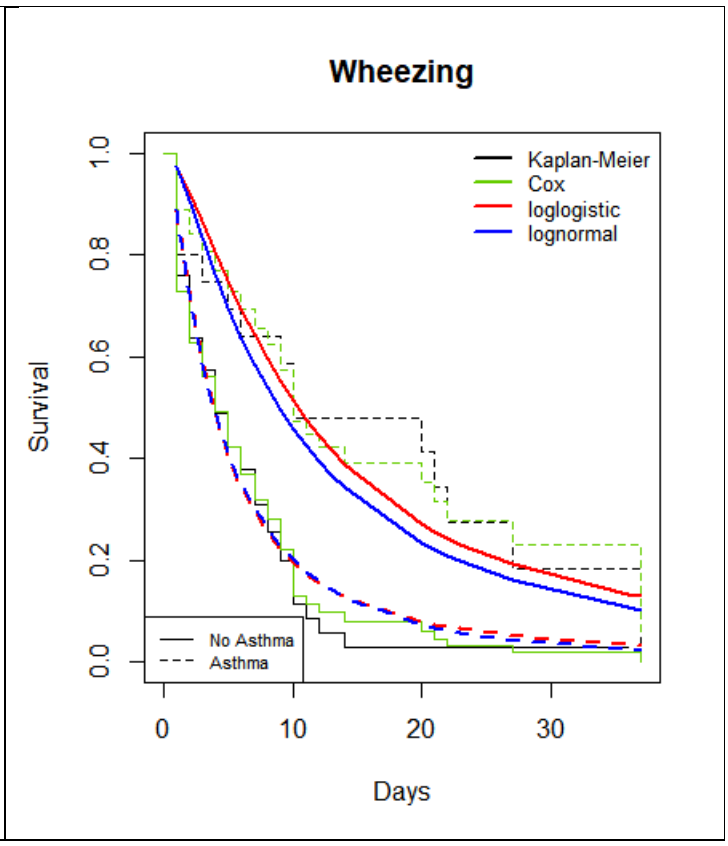
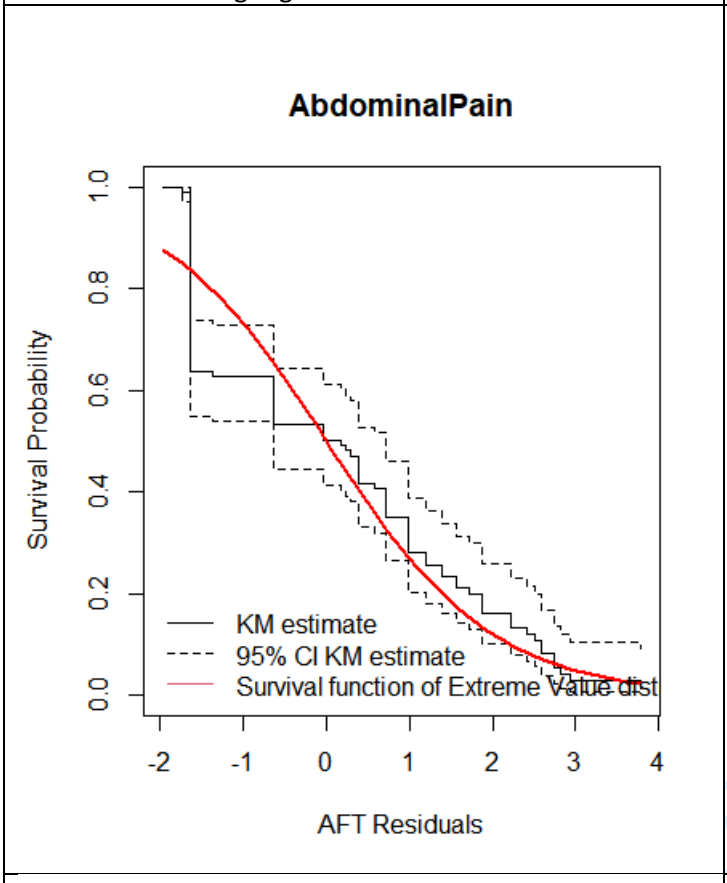
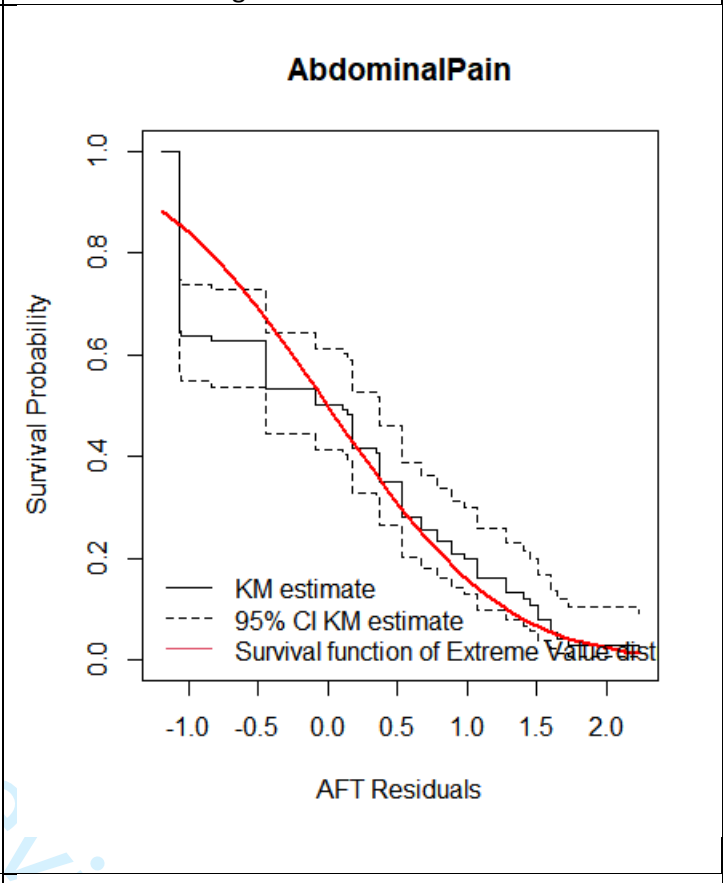
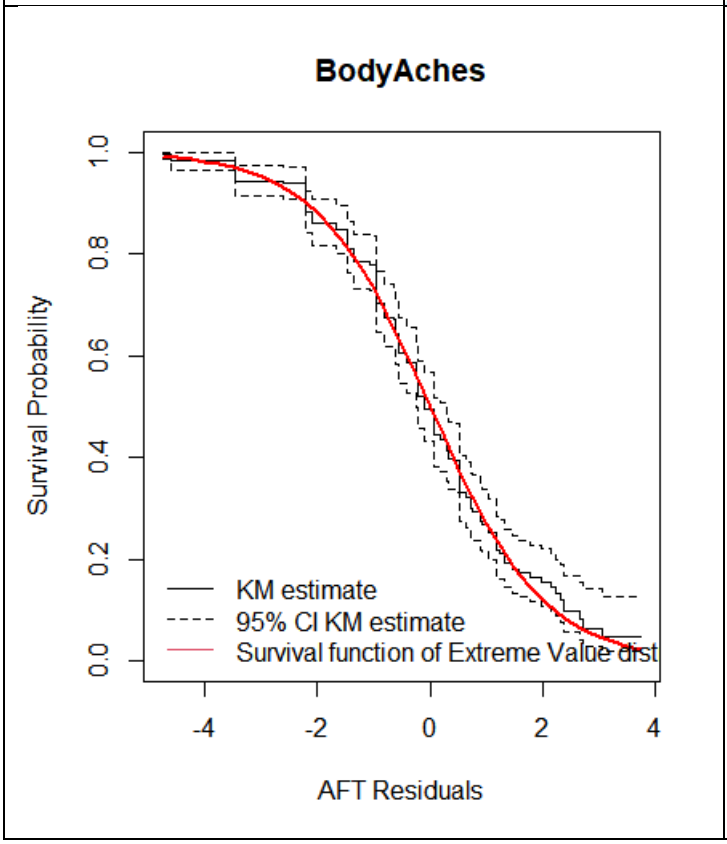
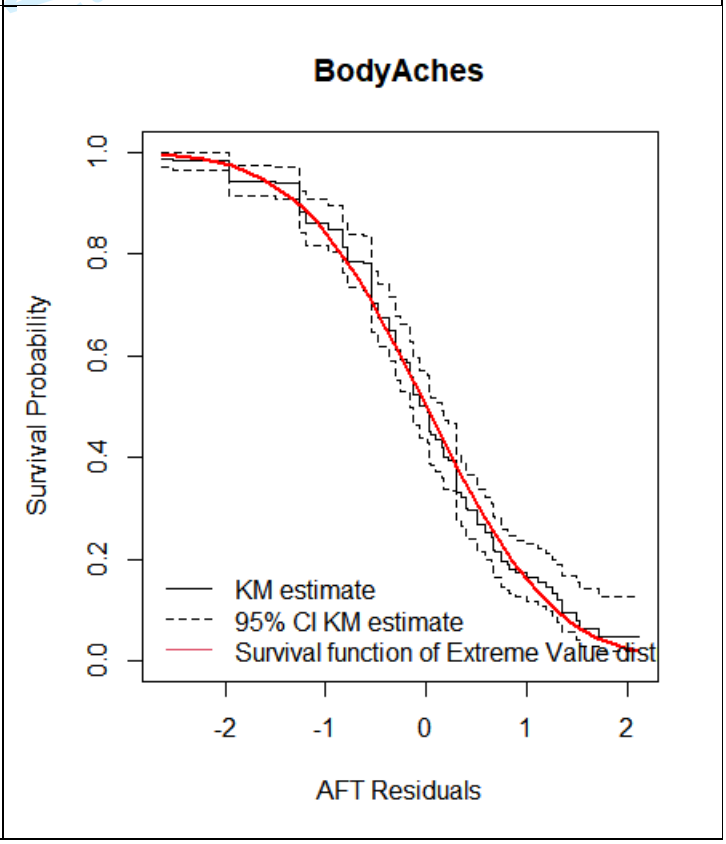
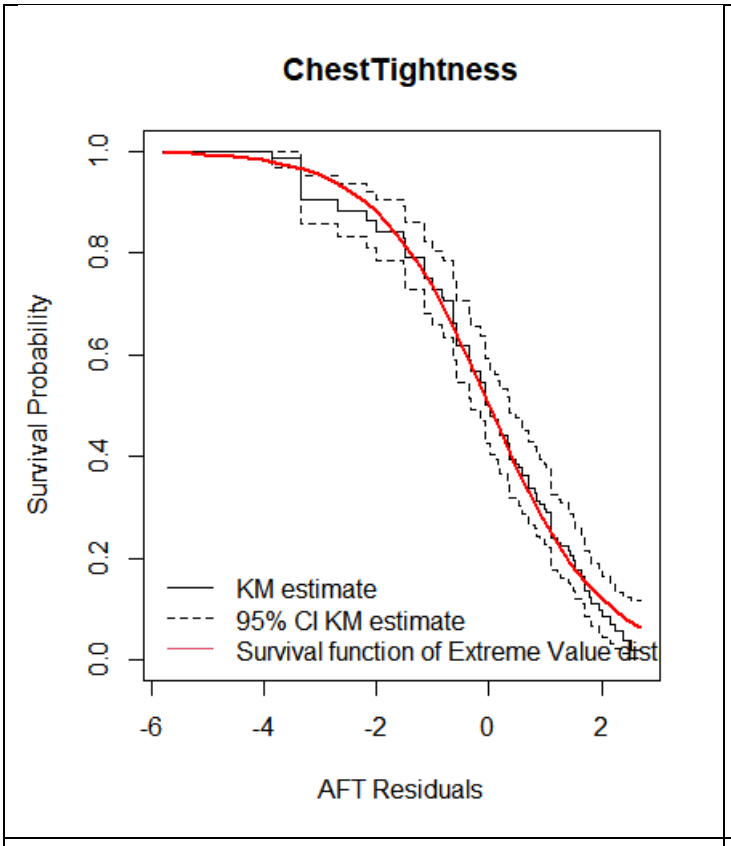
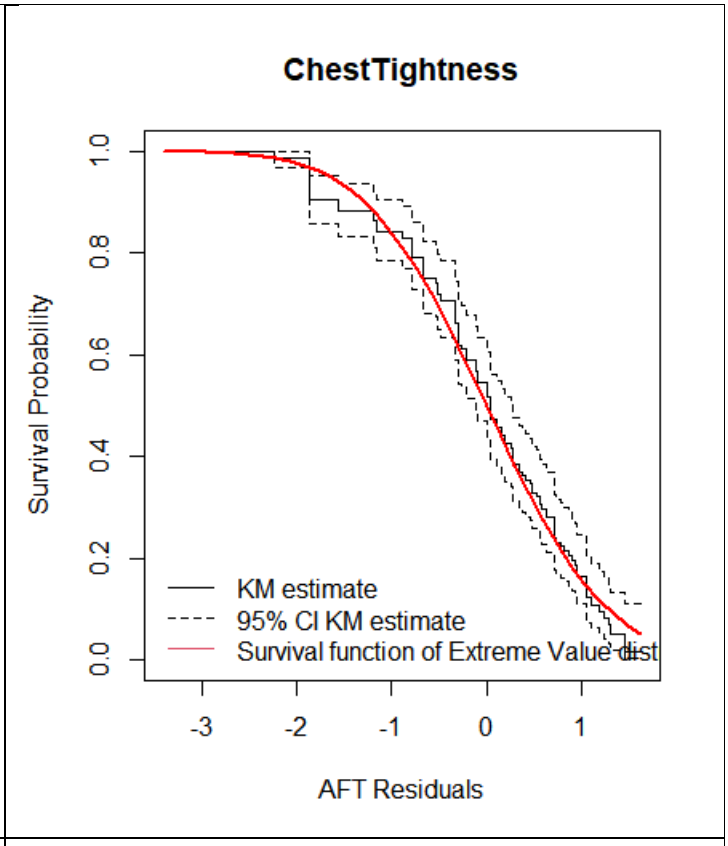



Figure 2 Goodness of fit, Kaplan Meier estimation of residual plotted against log-logistic and log-normal distribution side by side for comparison

| AFT model with log-logistic distribution | AFT model with log-normal distribution |
|---|---|
|  |  |
|  |  |


ChestTightness
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-6
-4
-2
0
2
AFT Residuals


ChestTightness
Survival Probability
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0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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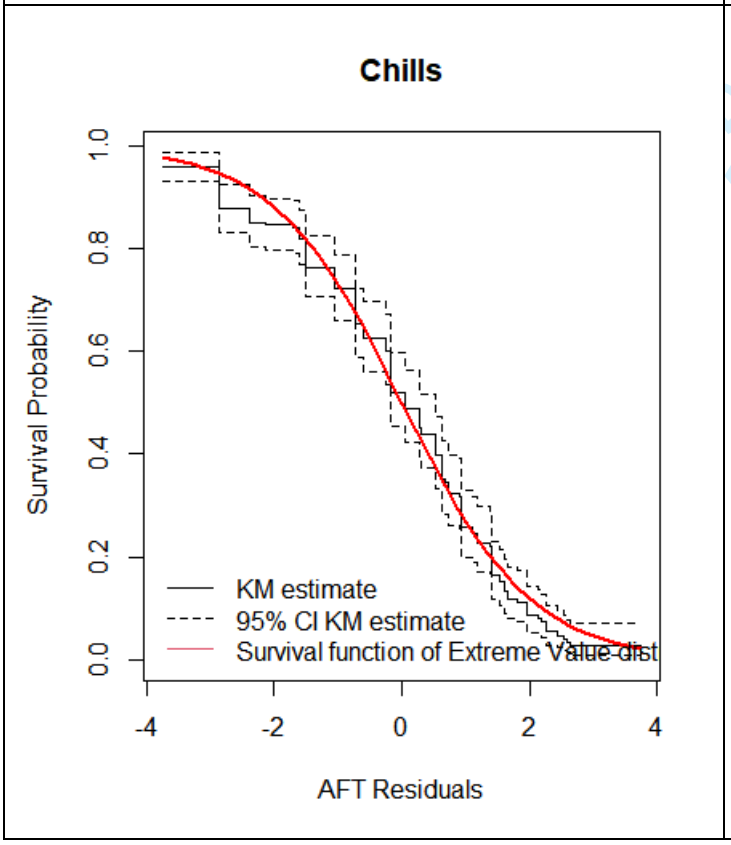
-2
-1
0
1
AFT Residuals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Survival Probability
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0.4
0.6
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KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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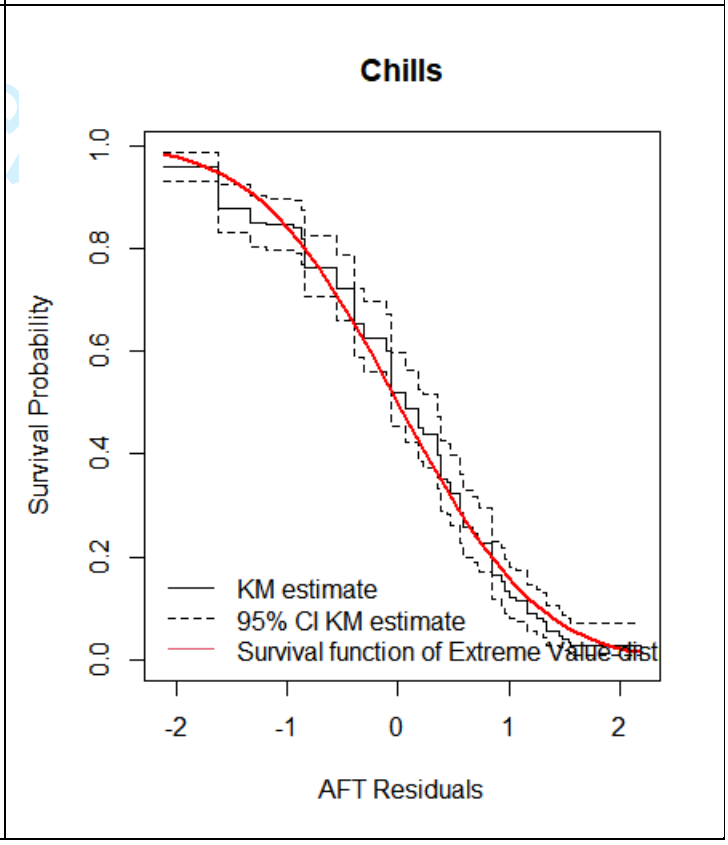
-2
0
2
4
AFT Residuals


Chills
Survival Probability
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0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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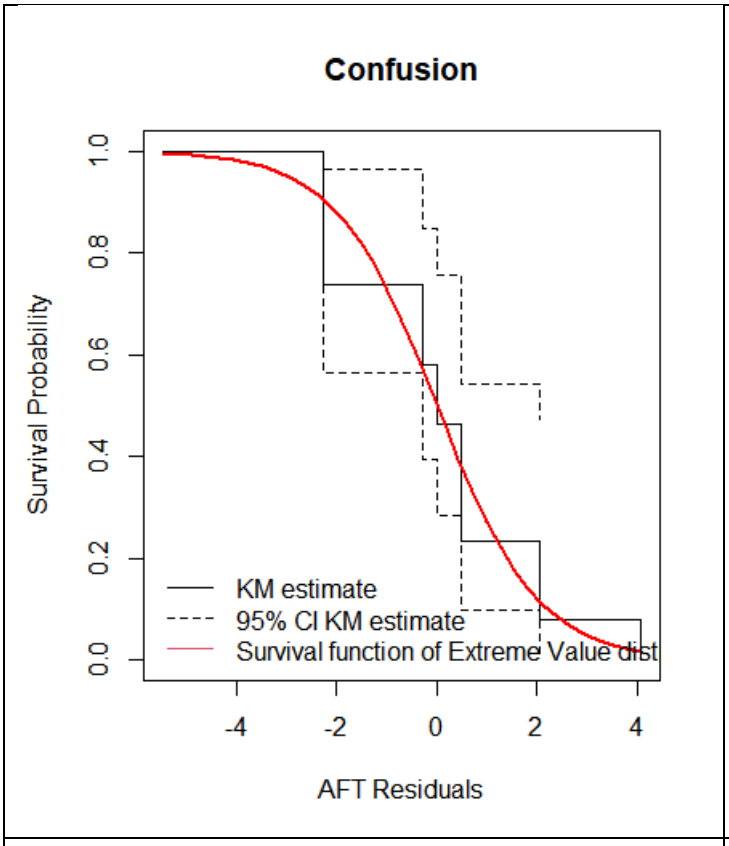
-1
0
1
2
AFT Residuals


Confusion
Survival Probability
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0.2
0.4
0.6
0.8
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KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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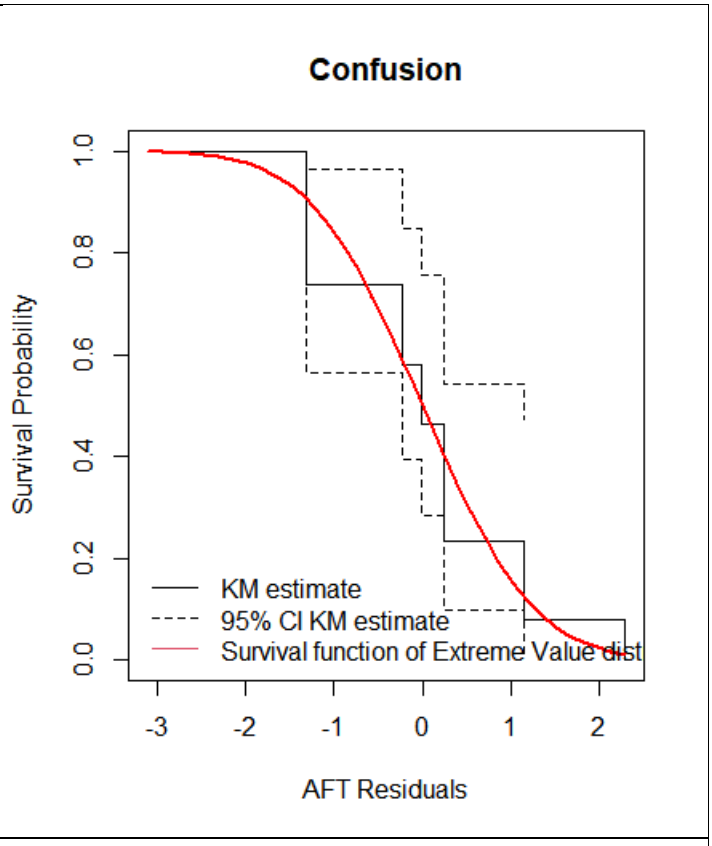
-2
0
2
4
AFT Residuals


Confusion
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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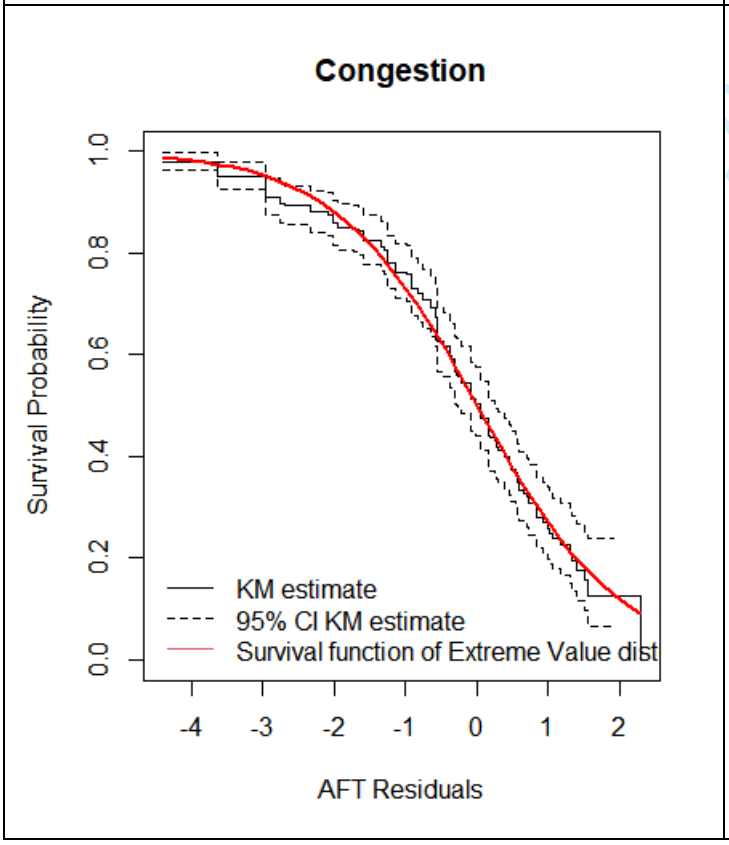
-2
-1
0
1
2
AFT Residuals


Congestion
Survival Probability
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KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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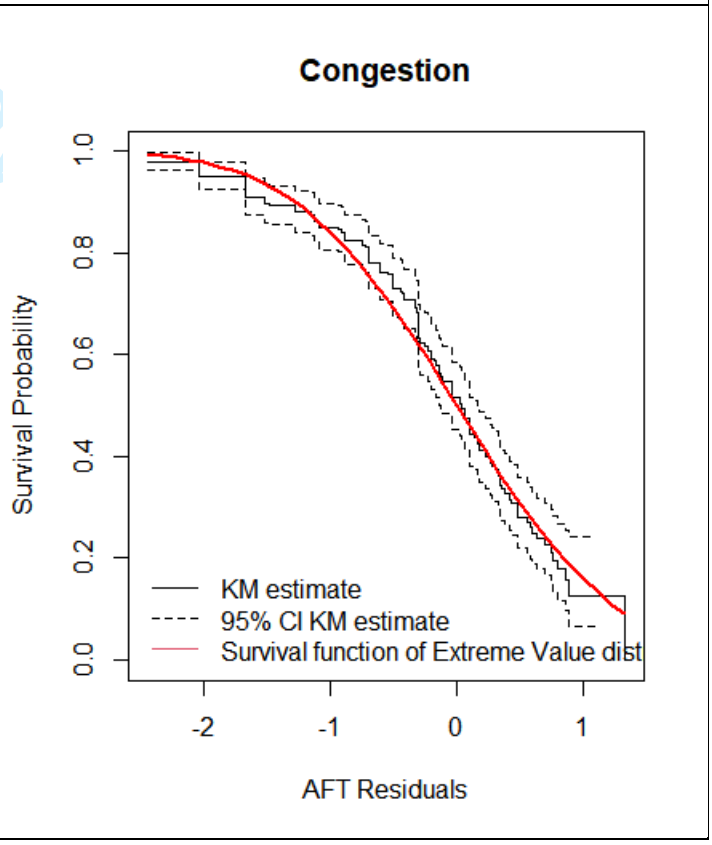
AFT Residuals


Congestion
Survival Probability
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0.2
0.4
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1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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0
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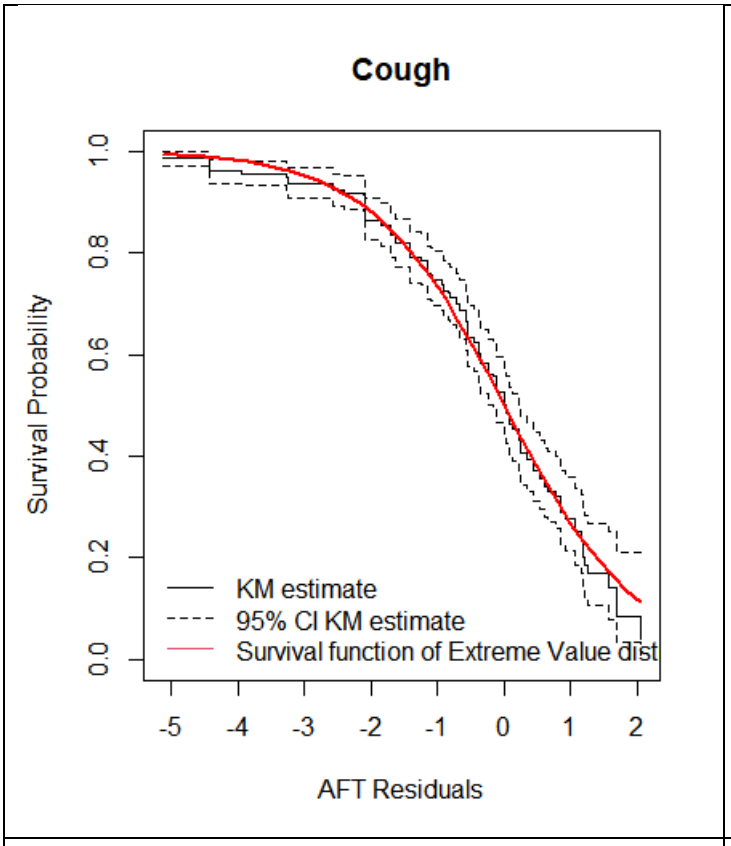
AFT Residuals


Cough
Survival Probability
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0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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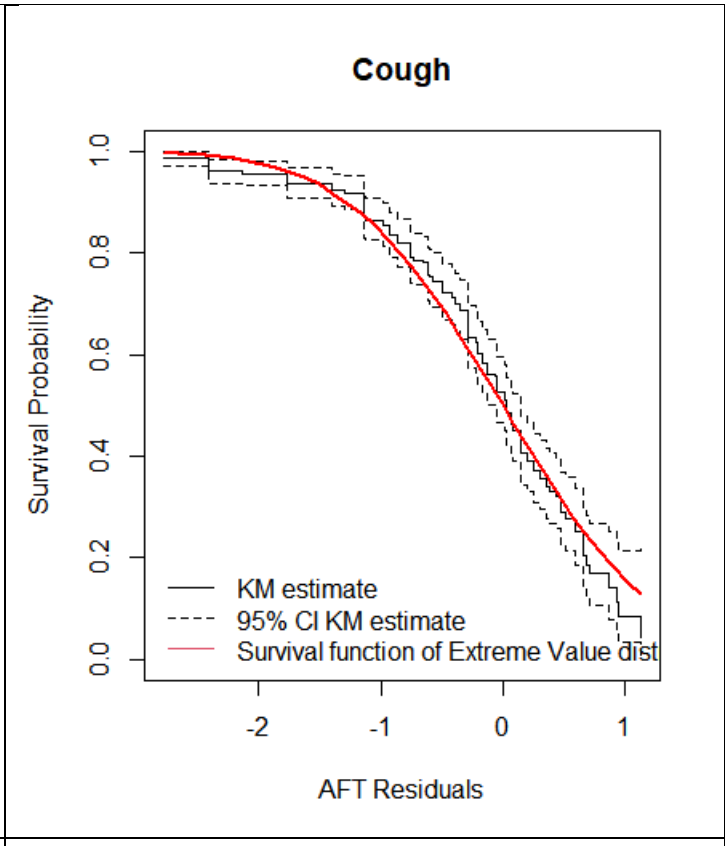
-4
-3
-2
-1
0
1
2
AFT Residuals


Cough
Survival Probability
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0.4
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KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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0
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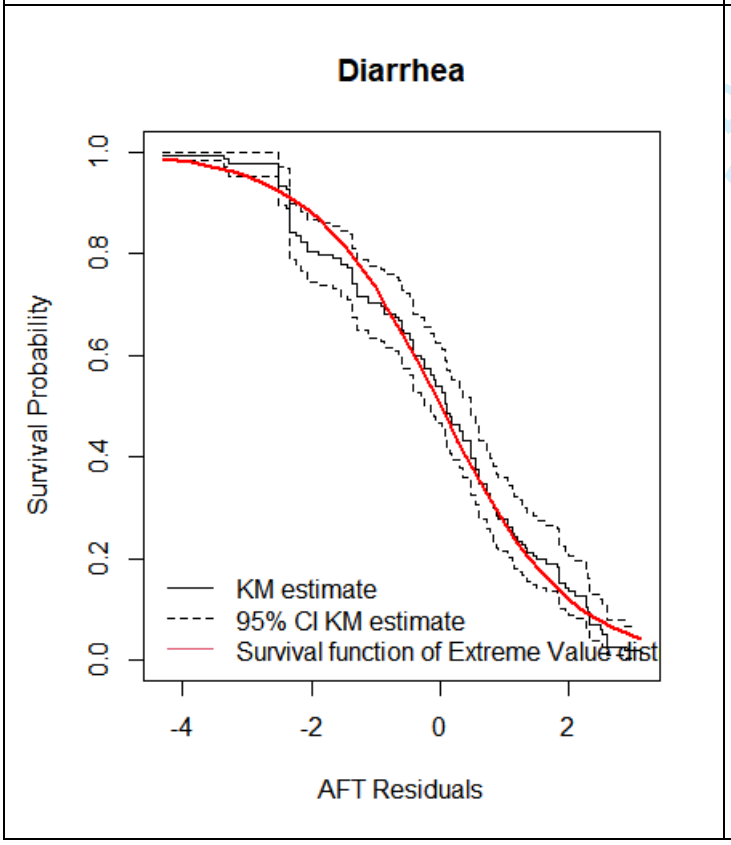
AFT Residuals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Survival Probability
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0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
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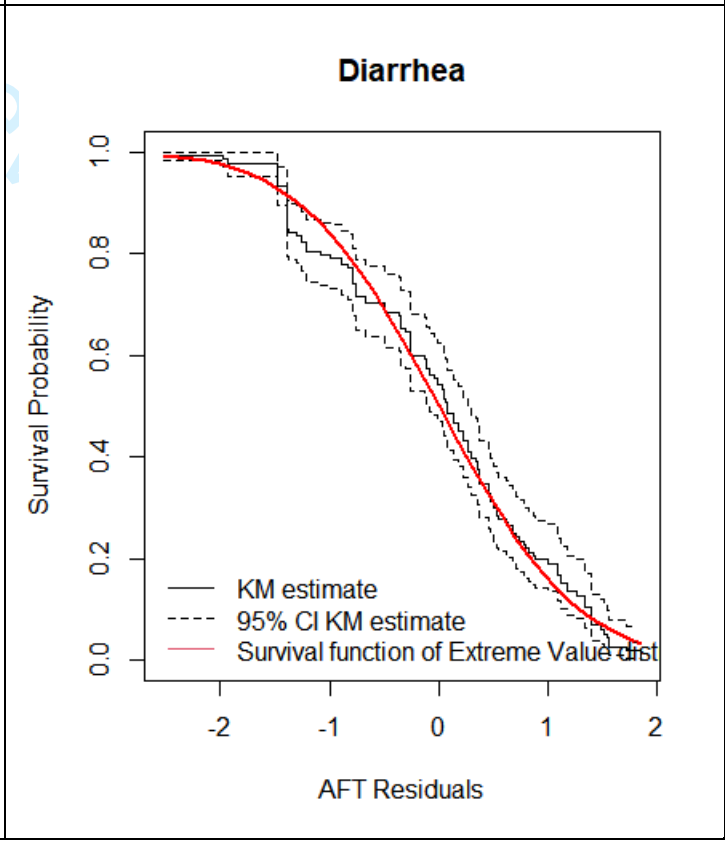
-2
0
2
AFT Residuals


Diarrhea
Survival Probability
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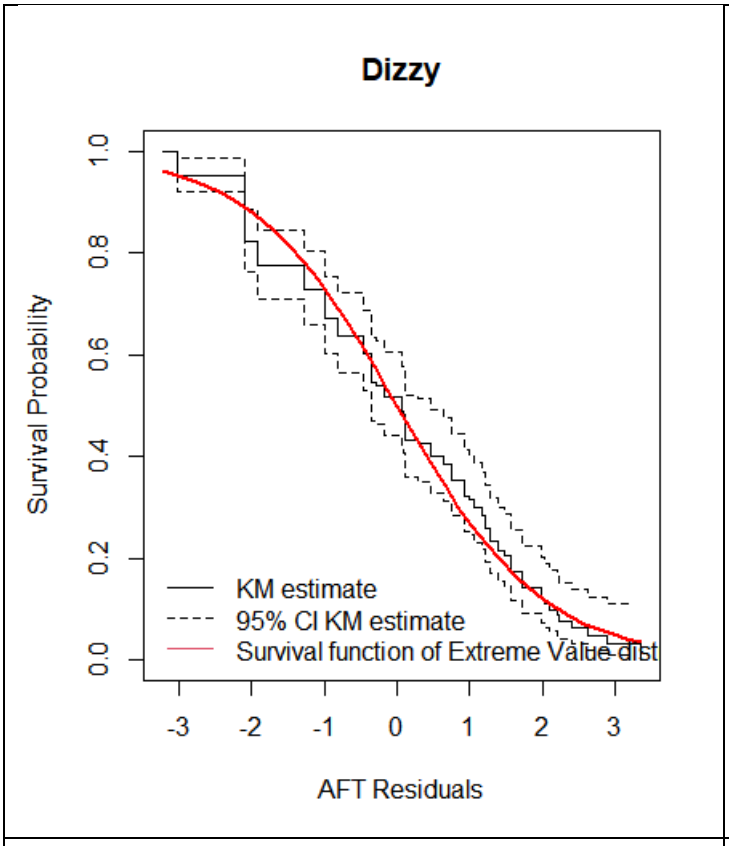
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2
-1
0
1
2
AFT Residuals


Dizzy
Survival Probability
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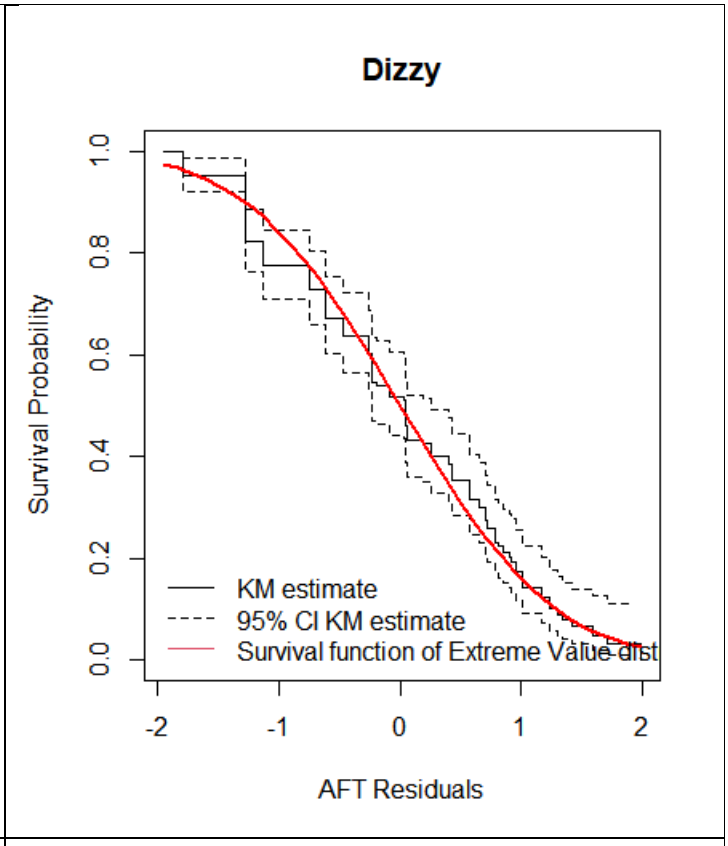
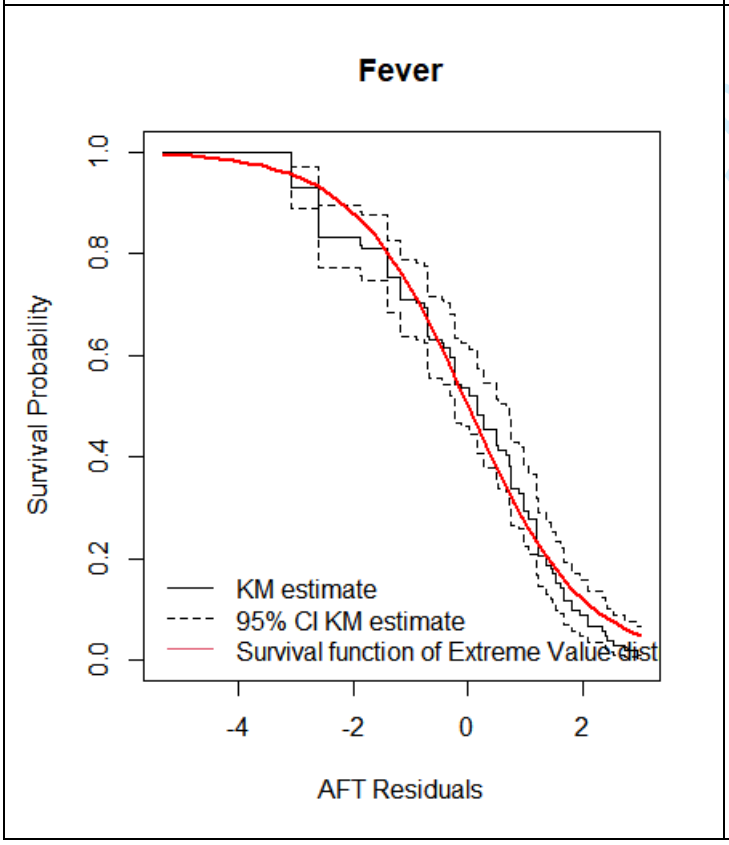
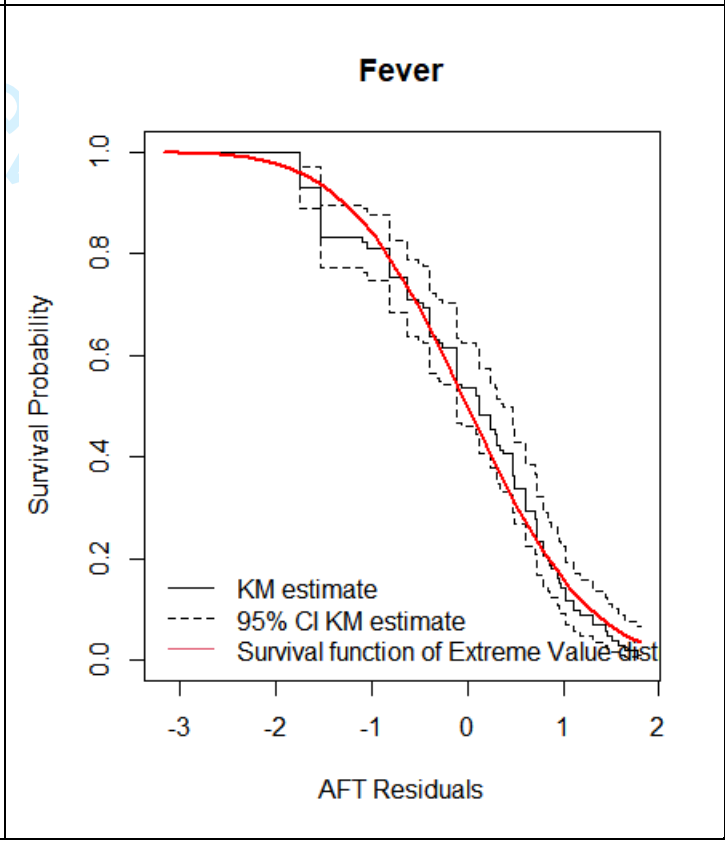
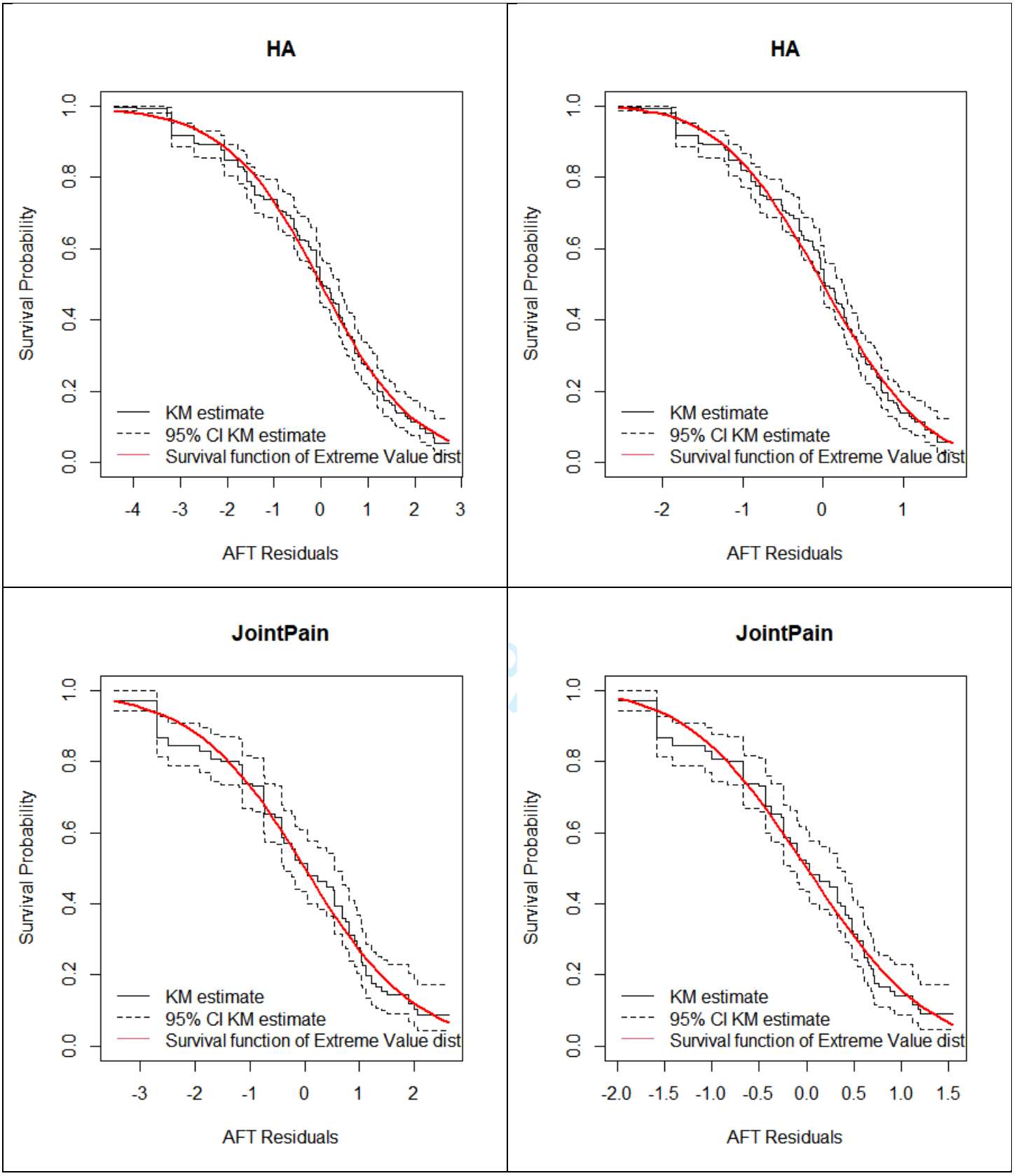
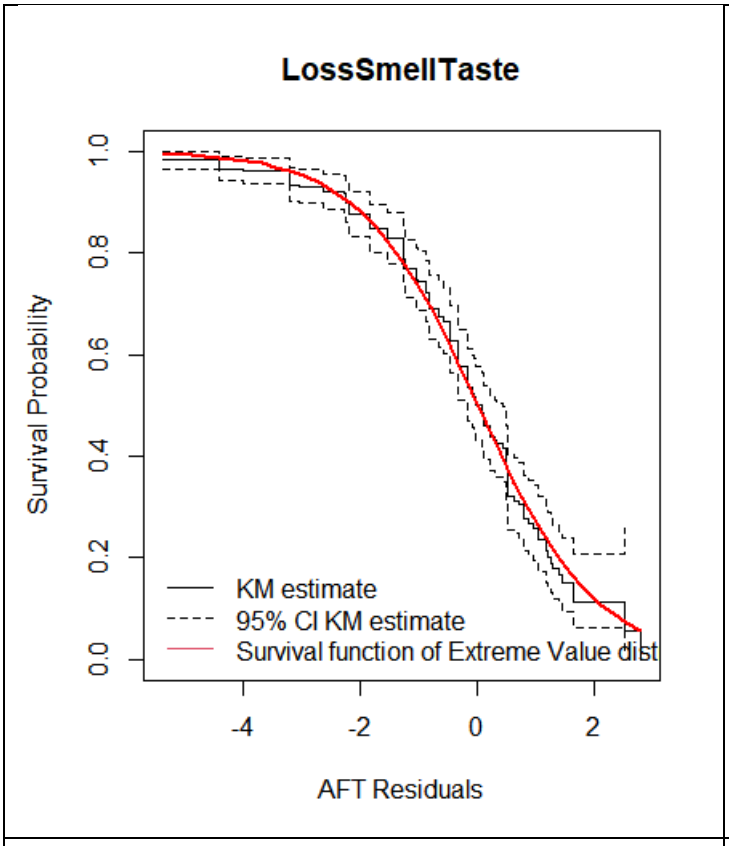
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
3
AFT Residuals

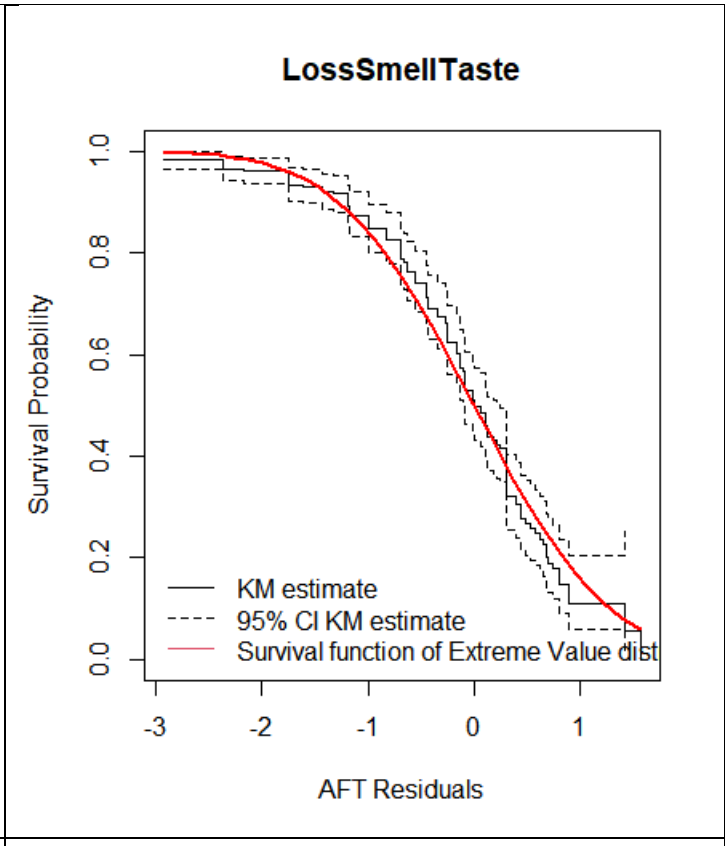

Dizzy
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2
-1
0
1
2
AFT Residuals

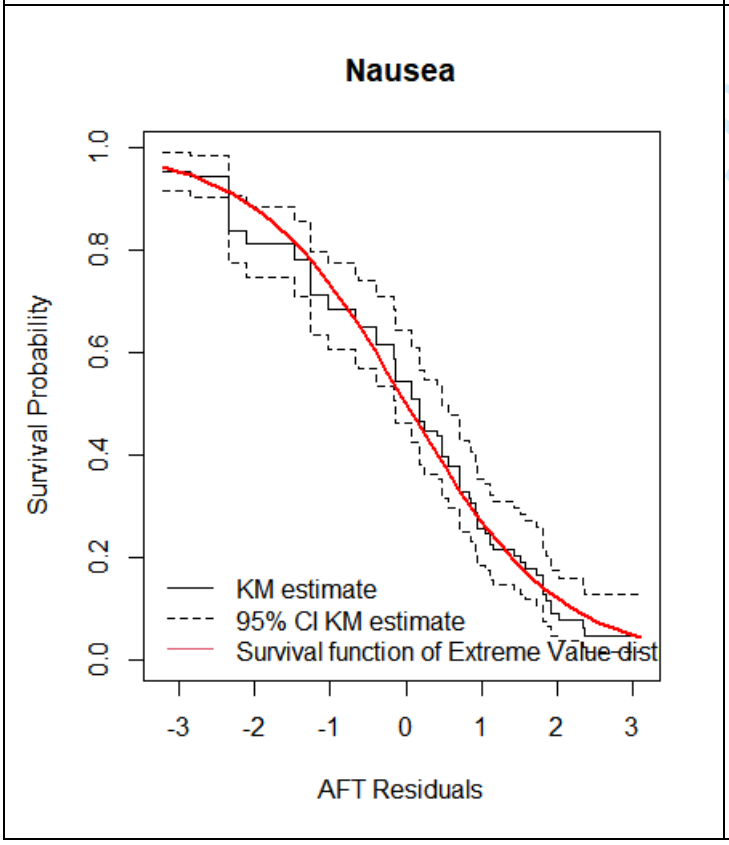

Fever
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-2
0
2
AFT Residuals

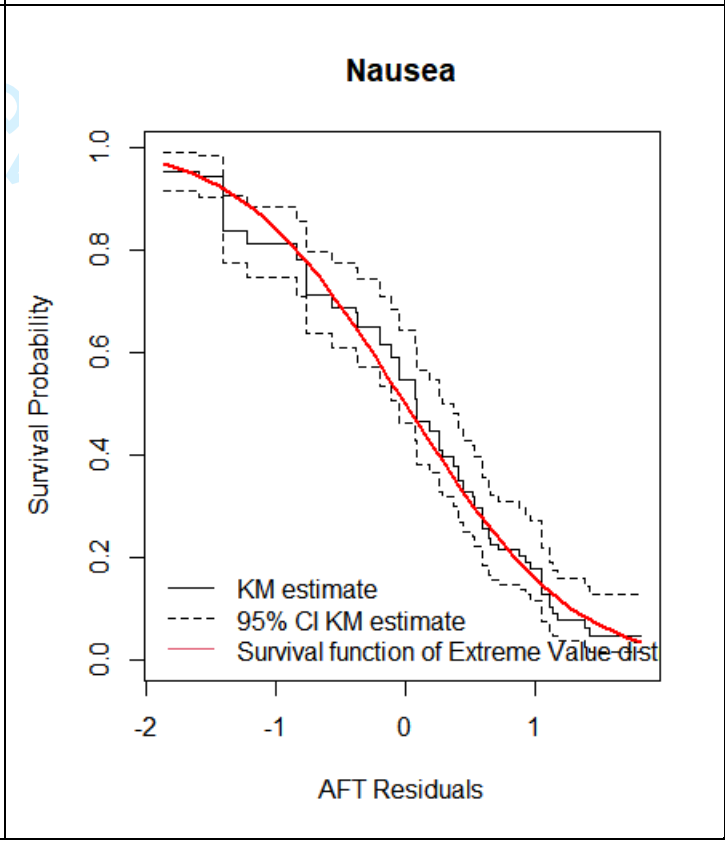

Fever
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
AFT Residuals

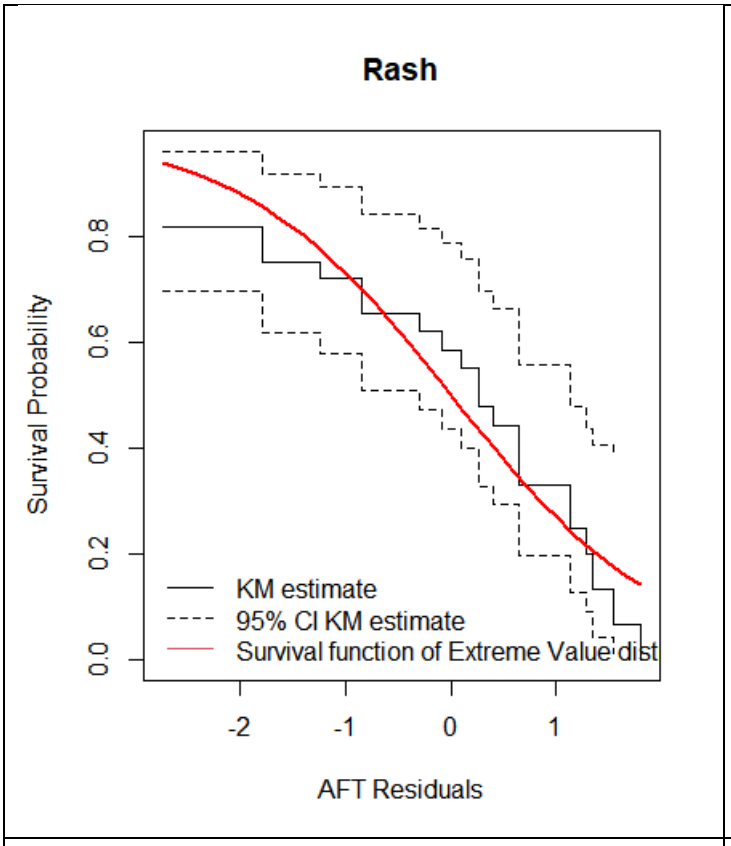

HA
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-3
-2
-1
0
1
2
3
AFT Residuals
HA
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2
-1
0
1
AFT Residuals
JointPain
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
AFT Residuals
JointPain
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2.0
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.5
AFT Residuals

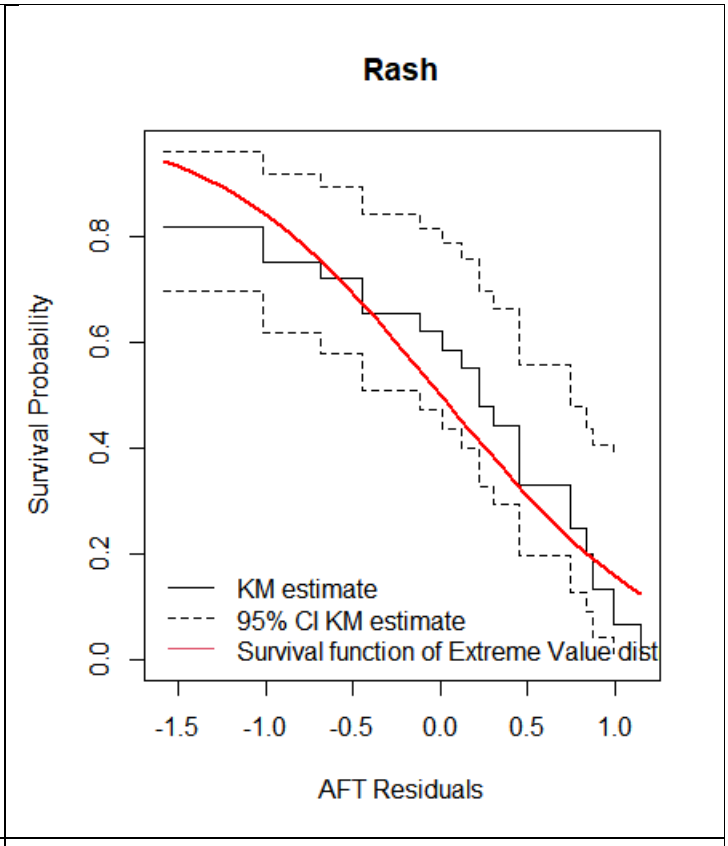

LossSmellTaste
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-4
-2
0
2
AFT Residuals

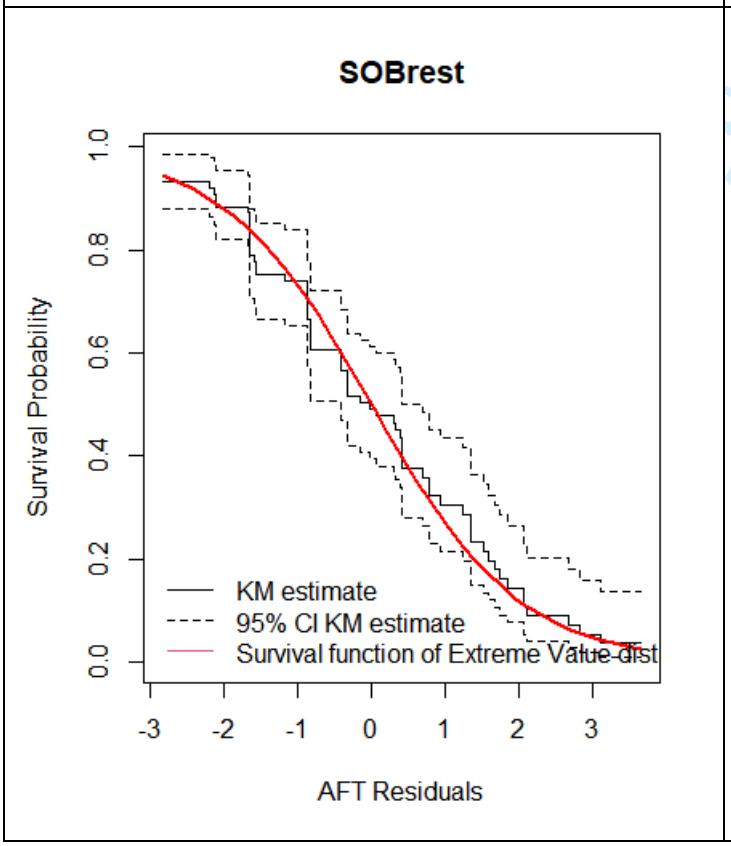

LossSmellTaste
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
AFT Residuals

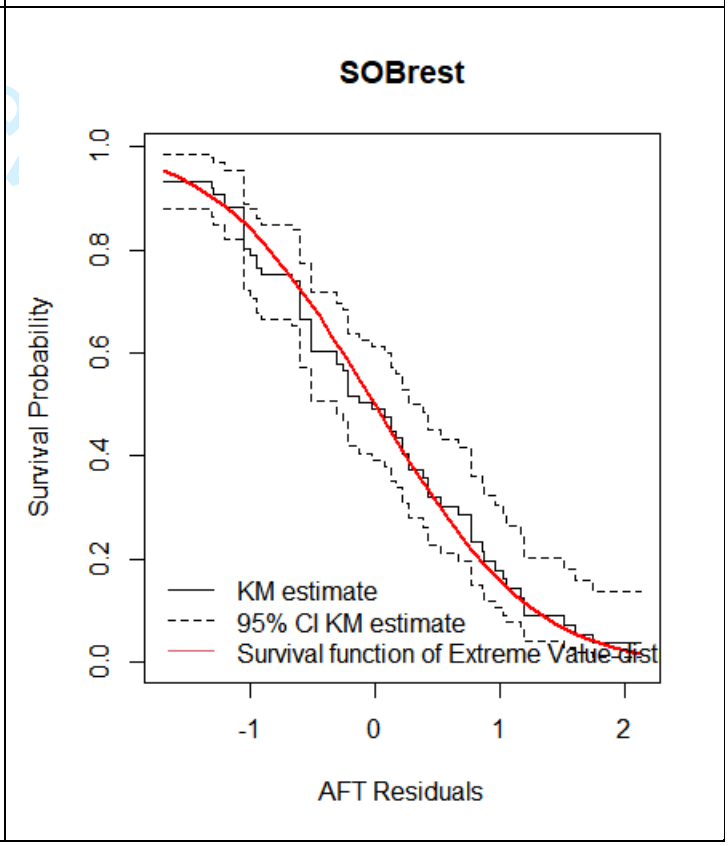

Nausea
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
3
AFT Residuals

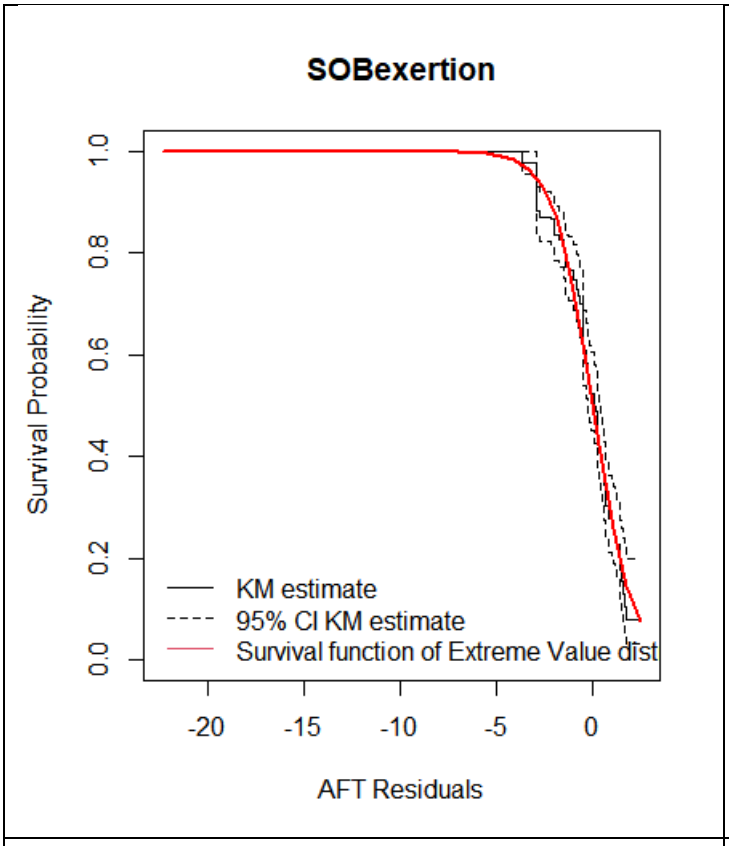

Nausea
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2
-1
0
1
AFT Residuals

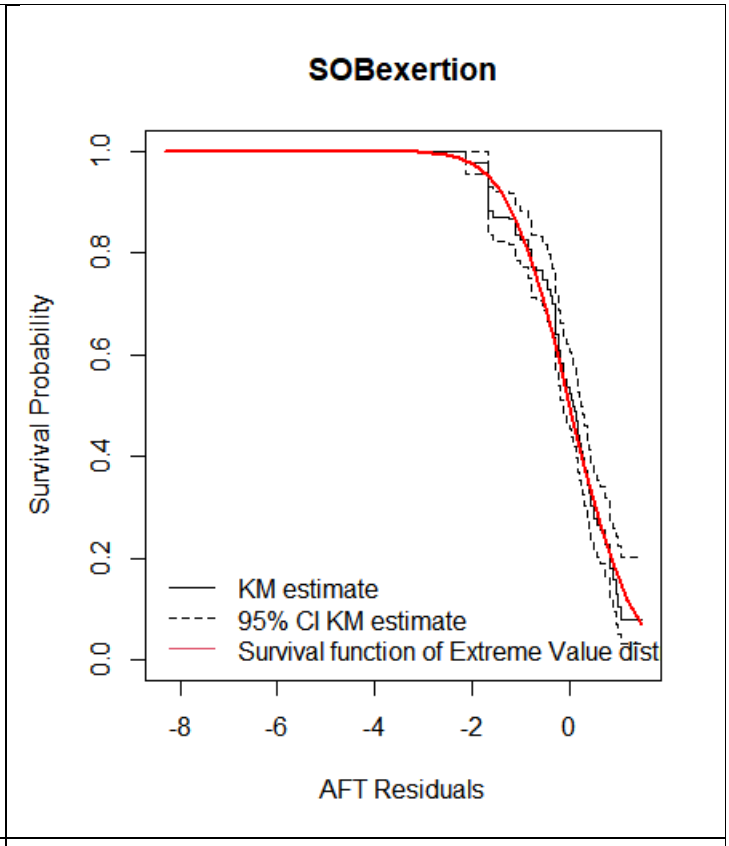

Rash
Survival Probability
0.0
0.2
0.4
0.6
0.8
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2
-1
0
1
AFT Residuals

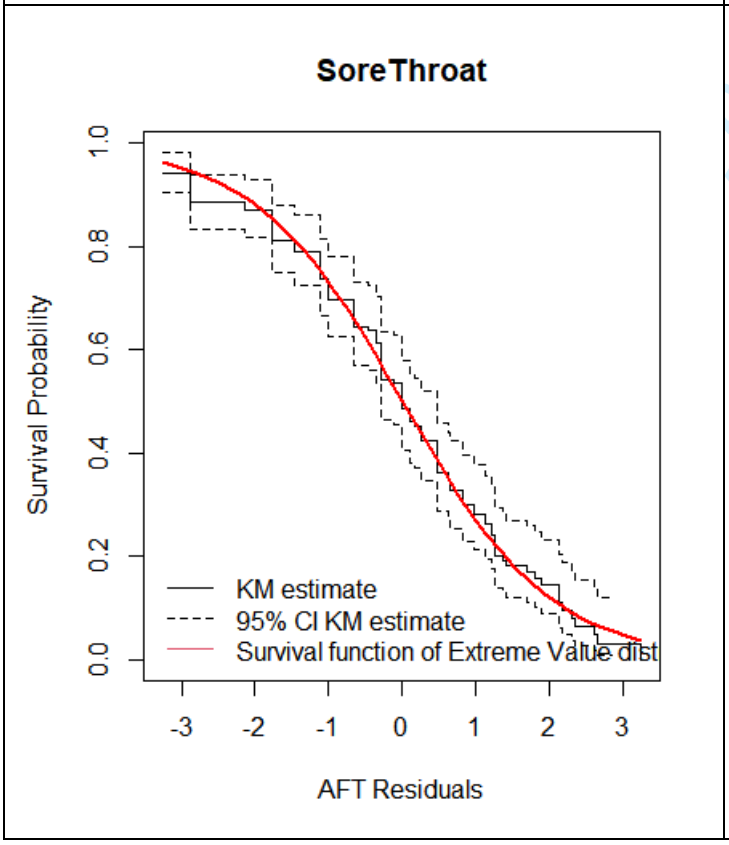

Rash
Survival Probability
0.0
0.2
0.4
0.6
0.8
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-1.5
-1.0
-0.5
0.0
0.5
1.0
AFT Residuals

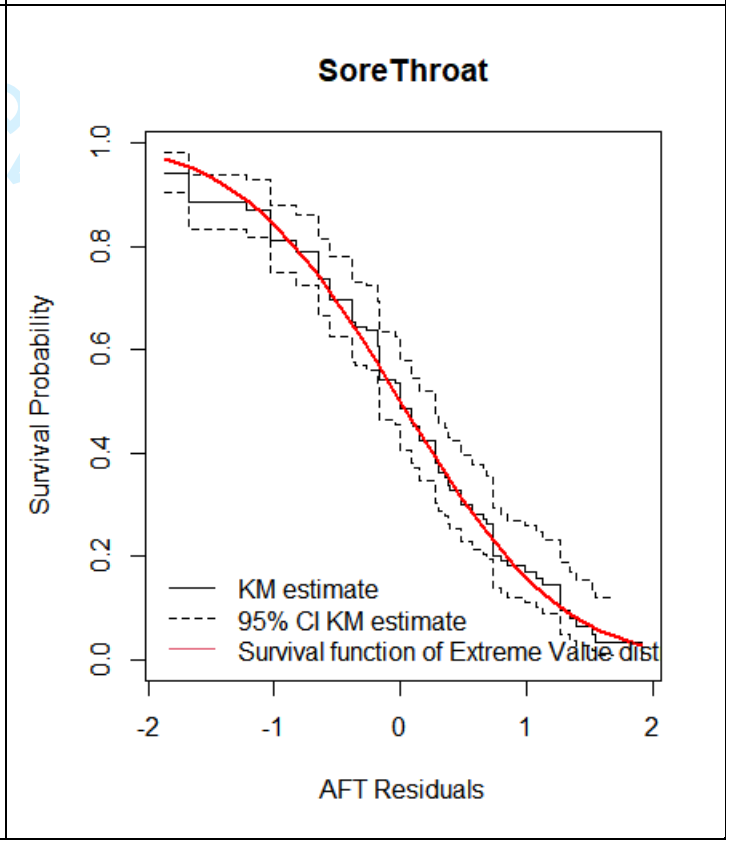

SOBrest
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
3
AFT Residuals

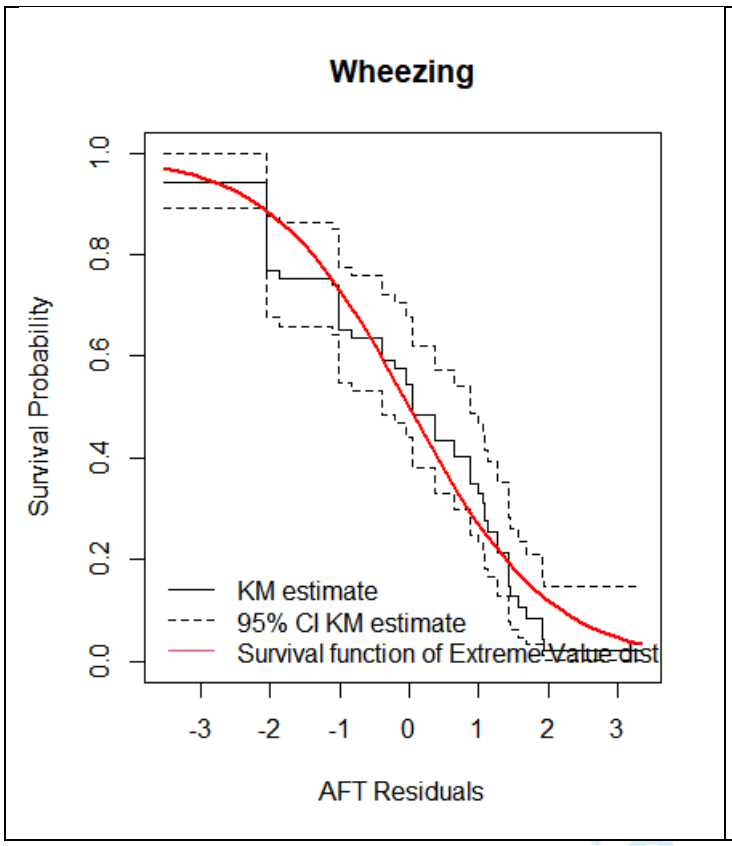

SOBrest
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-1
0
1
2
AFT Residuals

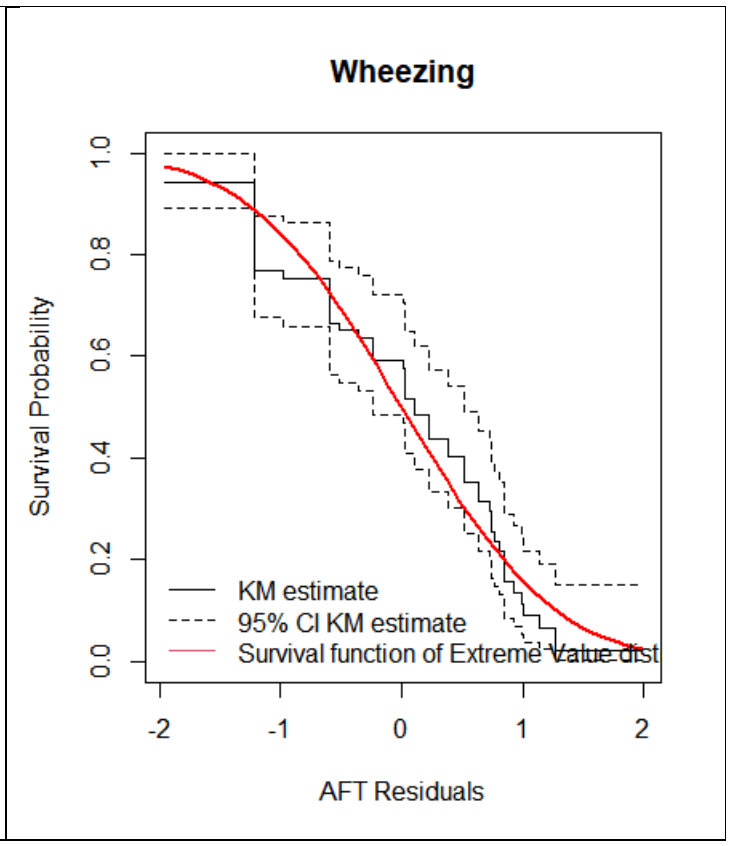

SOBexertion
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-20
-15
-10
-5
0
AFT Residuals


SOBexertion
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-8
-6
-4
-2
0
AFT Residuals


SoreThroat
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-3
-2
-1
0
1
2
3
AFT Residuals


SoreThroat
Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
KM estimate
95% CI KM estimate
Survival function of Extreme Value dist
-2
-1
0
1
2
AFT Residuals



STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract<br>(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 1-2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 4-5 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 6 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 6 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>(*b*) For matched studies, give matching criteria and number of exposed and unexposed | 6 |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 7-10 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 8-9 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 10 |
| Study size | 10 | Explain how the study size was arrived at | 6 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 9-10 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding<br>(*b*) Describe any methods used to examine subgroups and interactions<br>(*c*) Explain how missing data were addressed<br>(*d*) If applicable, explain how loss to follow-up was addressed<br>(*e*) Describe any sensitivity analyses | 10-11 |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram | 12 |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) Summarise follow-up time (eg, average and total amount) | 12-14 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 14-16 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 16 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | NA |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 17-18 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 19-20 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 18-19 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 20 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | NA |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.