Dissecting clinical features of COVID-19 in a cohort of 21,312 acute care patients

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Abstract

Background Although, COVID-19 has resulted in over 7 million deaths globally, many questions still remain about the risk factors for disease severity and the effects of variants and vaccinations over the course of the pandemic. To address this gap, we conducted a retrospective analysis of electronic health records from COVID-19 patients over 2.5 years of the COVID-19 pandemic to identify associated clinical features.

Methods We analyze a retrospective cohort of 21,312 acute-care patients over a 2.5 year period and define six clinical trajectory groups (TGs) associated with demographics, diagnoses, vitals, labs, imaging, consultations, and medications.

Results We show that the proportion of mild patients increased over time, particularly during Omicron waves. Additionally, while mild and fatal patients had differences in age, age did not distinguish patients with severe versus critical disease. Furthermore, we find that both male sex and Hispanic/Latino ethnicity are associated with more severe/critical TGs. More severe patients also have a higher rate of neuropsychiatric diagnoses and consultations, along with an immunological signature of high neutrophils and immature granulocytes, and low lymphocytes and monocytes. Interestingly, low albumin is one of the best lab predictors of COVID-19 severity in association with higher malnutrition in severe/critical patients, raising concern of nutritional insufficiency influencing COVID-19 outcomes. Despite this, only a small fraction of severe/critical patients had nutritional labs checked (e.g. Vitamin D, thiamine, B vitamins) or received vitamin supplementation.

Conclusions Our findings expand on clinical risk factors in COVID-19, and highlight the interaction between severity, nutritional status, and neuropsychiatric complications in acute care patients to enable identification of patients at risk for severe disease.

Plain Language Summary

We evaluated electronic health records collected over 2.5 years during the COVID-19 pandemic to identify diagnoses, clinical laboratory and imaging tests, vital signs, consultations, and medications that were associated with disease severity and mortality, including how these associations changed across different SARS-CoV-2 strains. We found neuropsychiatric complications, and nutritional insufficiency to be key factors in disease severity, which suggest that patients' neurological, psychiatric and nutritional status should be evaluated early in COVID-19 to help identify those at risk of severe disease outcomes.

The coronavirus disease 2019 (COVID-19) pandemic has caused an estimated 645 million hospitalizations and over 7 million deaths globally[1]. Although COVID-19 mainly affects the respiratory system, it can also cause multi-system damage[2]. While multiple studies have identified risk factors for COVID-19 respiratory severity[3–5], the rates of non-respiratory complications remain unclear. Furthermore, most COVID-19 studies have focused on hospitalized patients[3,6–8], leaving a knowledge gap in the clinical features of non-hospitalized patients evaluated in acute care facilities, such as the emergency department (ED).

Additionally, critical questions remain regarding patient outcomes in association with different circulating SARS-CoV-2 strains between 2019 and 2022[9]. Notably, Omicron strains have been linked to less severe disease compared to earlier strains, attributed to either lower virulence and/or immunity from vaccinations and prior infections[10]. However, it remains undetermined how specific clinical features have differed in patients with Omicron compared to earlier strains and whether there is a difference in clinical co-morbidities across different SARS-CoV-2 strains.

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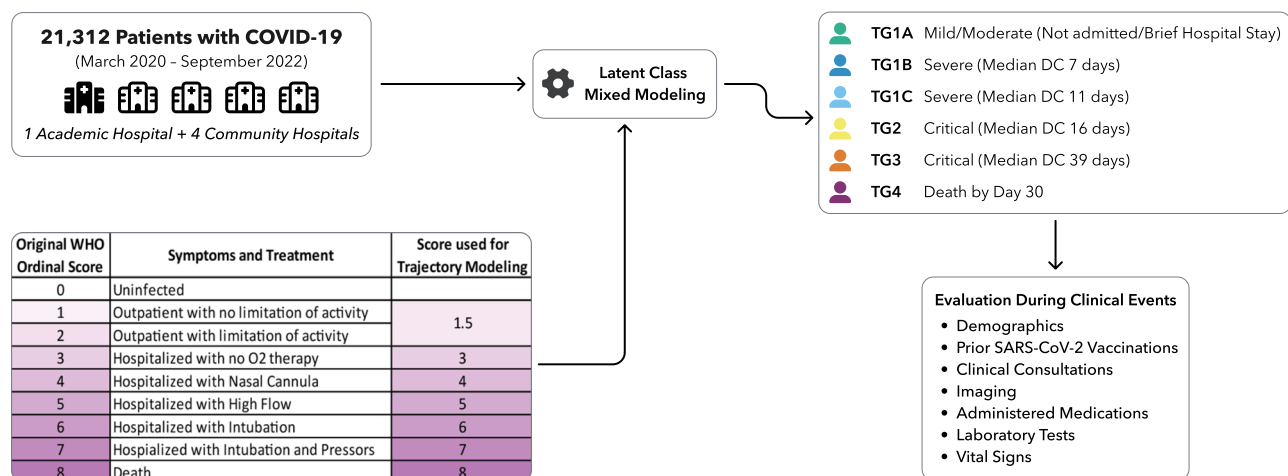
Fig. 1 | Experimental schema of analysis. Modeling of modified WHO ordinal scale identified six trajectory groups representative of increasing disease severity. Trajectory Group (TG) 1 consisted of mild/moderate patients who were evaluated in the ED, but not admitted; TG1B and TG1C represented severe hospitalized patients with short discharge; TG2 and TG3 were made up of critical patients with longer hospitalization, and TG4 was made up of fatal patients.

To address these questions, we examine a 2.5-year retrospective cohort of 21,312 COVID-19 patients at five hospital EDs in Central Texas. We identify 6 distinct patient trajectory groups (TGs) and their unique clinical features and characterize how these TGs change overtime during the COVID-19 pandemic. Our results expand upon clinical risk factors for COVID-19 severity in both hospitalized and ED-evaluated patients and provide insights into salient clinical features for COVID-19 patient outcomes.

Methods

Study approval and data collection
The UT Austin Institutional Review Board (IRB ID: 2020-04-0117) and Ascension Seton (CR-20-066) approved the study and waived consent for the retrospective analysis due to data being de-identified for analyses, and collectively posing minimal risk. Electronic Health Record (EHR) data were extracted in October 2022 for 21,312 COVID-19 patients' records that occurred between March 2020 and September 2022 in Central Texas from the Ascension Seton Hospital Network clinical data warehouse with support and data sharing processes of the Dell Medical School Enterprise Data Intelligence Team[11]. The Central Texas Seton Hospital network consisted of 1 academic medical center and 4 community hospitals spanning Travis, Hays and Williamson counties. Patients were included based on having a COVID-19 (U07.1) diagnosis code with all events being referenced to the patient's first acute care event related to their first COVID-19 diagnosis code. Funding sources did not have a direct role in design, analysis, or approval of this manuscript.

World health organization ordinal scale
Patients were retrospectively scored daily based on oxygen status, adapting the World Health Organization (WHO) COVID19 Ordinal Scale[12] (Fig. 1), classified as: 1 = asymptomatic, 2 = mild limitation in activity, 3–4 = hospitalized with mild/moderate disease (3 = room air/ 4 = nasal cannula or facemask oxygen), 5–7 = hospitalized with severe disease (5 = high-flow nasal cannula or noninvasive ventilation, 6 = intubation/mechanical ventilation, 7 = intubation/mechanical ventilation and organ failure), 8 = death. Scores of 1 and 2 were combined into 1.5 due to lack of outpatient data to quantify limitation of activity.

Latent class mixed modeling and statistical testing
Latent class mixed modeling (LCM) (R package lcmm (v2.0.0)) (Supplementary Fig. 1A–D)[13] was used to identify patient TGs for the modified WHO ordinal score over the course of 30 days with the final model using a quadratic fixed and main effect: fixed = value ~ trajectory_group + I(trajectory_group^2), random = ~ trajectory_group + I(trajectory_group^2)) andadditional details in the Supp. Methods. Participants were assigned to the TG they had the greatest probability for, with this probability on average being above 95% for each group (Supplementary Fig. 1E). Additionally, the LCM derived groups were compared to groups derived from group-based trajectory analysis (GBTA)[14], which identified similar TGs (see Supplemental Methods and Supplementary Fig. 1F–I). To differentiate TG1 trajectories, LCM was repeated with TG1 patients over a 12-day period, identifying TG1A/TG1B/TG1C subclasses. Central Texas reported COVID-19 case counts and vaccination data was retrieved from the county data portal[15]. Waves 1–5 were divided by county-reported cases.

Statistics and reproducibility
Generalized linear modeling was used to simultaneously evaluate all demographic variables reported in Supplementary Table 1 while controlling for their interaction with age. Chi-square testing was used to identify changes in the overall rate of diagnoses and consultations by the identified COVID-19 waves (Supplementary Data 2–3). Diagnoses, imaging, consultations, administered medications, as well as laboratory tests and vital signs within the first two days of admission were evaluated via cumulative linked modeling using the ordinal R package (v2022.11.16)[16]. For comparison of pairwise TG clinical features, significance was calculated using Chi-square testing (Supplementary Data 4–9). Longitudinal changes were evaluated with Generalized Additive Mixed Modeling using R package gamm4 (v0.2.6) (Supplementary Data 10 and 11)[17]. Analyses controlled for hospital site, year/yearly quarter, sex, age, ethnicity, and race. The values for absolute lymphocytes, monocytes, neutrophils, eosinophils, immature granulocytes, basophils, white blood cells, and platelets were log transformed prior to generalized additive mixed modeling. All analyses were Bonferroni adjusted for multiple hypothesis testing. Computational analyses were performed using the Biomedical Research Computing Facility at UT Austin, Center for Biomedical Research Support.RRID: SCR_021979. Source data for figures in this manuscript are provided as Supplementary Data 12.

Reporting summary
Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Results

Study cohort
We analyzed 21,312 patient records across 47,063 retrospective encounters from five hospitals in Central Texas between March 2020 and September 2022 with the demographic features of the cohort displayed in
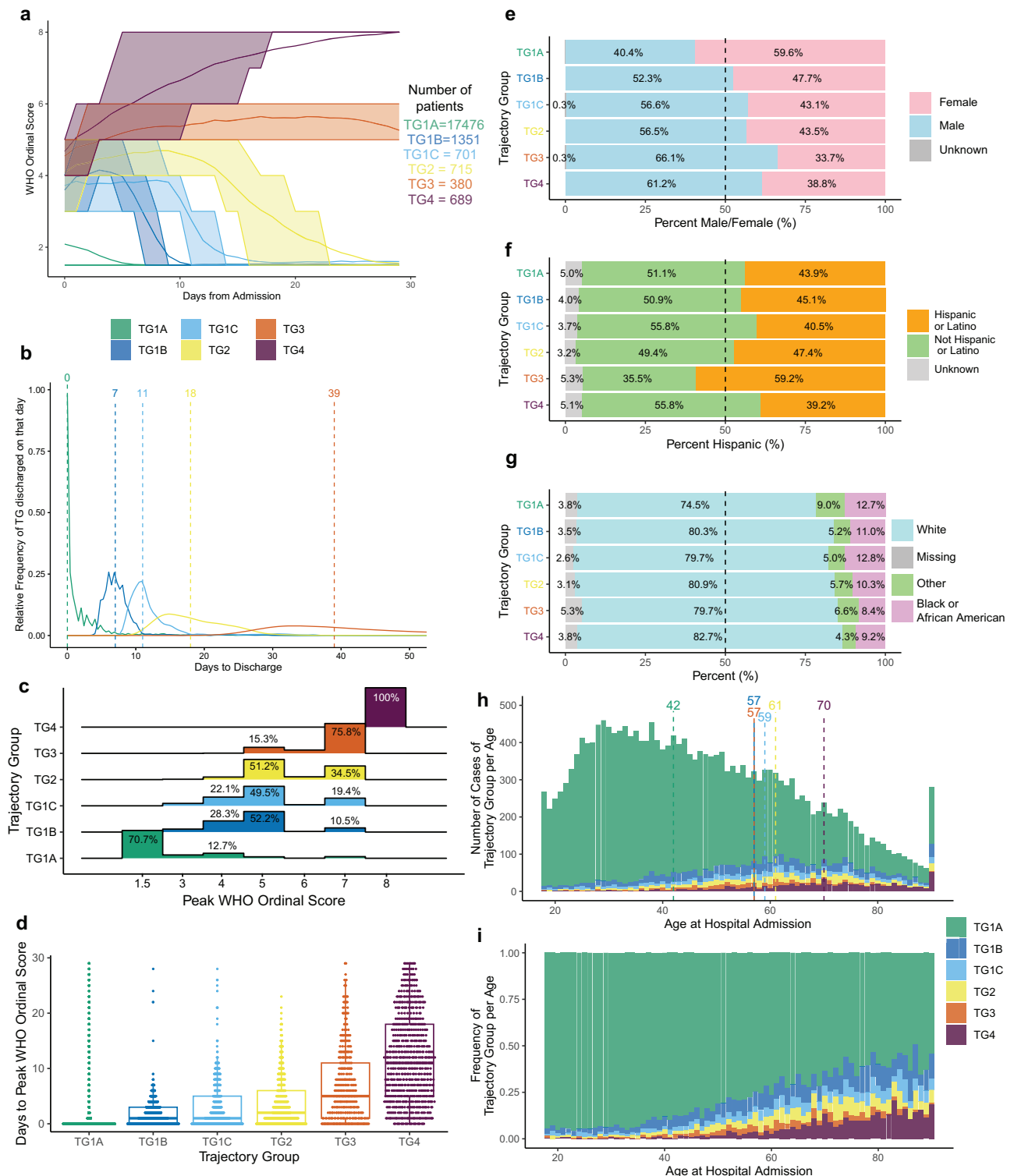
Fig. 2 | COVID-19 trajectory groups capture disease severity and reveal underlying demographic differences. a The average trajectory of the WHO ordinal scale for each trajectory group over 30 days, with shading indicating the interquartile range. **b** Distribution by trajectory group of days to discharge with the median of each group indicated by dotted line. **c** Distribution of the peak scores from the first 30 days of all participants in each trajectory group. **d** Box and whisker plot of the days to each patient's peak score by trajectory group. **e** Biological Sex, **f** ethnicity, and (**g**) racial composition of each trajectory group. **h** Histogram of the number of cases per trajectory group with age. Dotted lines denote the median age of each trajectory group. **i** Relative frequency of each trajectory group with age.

Supplementary Table 1 and Fig. 2. The 30-day mortality rate for all evaluated patients was 3.23%, with a mortality rate of 7.73% among only admitted patients, and a 17.96% mortality rate among only severe/critical patients (TG1B-TG4).

We identified four initial TGs on the modified WHO ordinal scale[12] over 30-days (Fig. 2A). To better capture acute hospitalization trajectories, TG1 was further divided into TG1A, TG1B, and TG1C by repeating modeling over only 12 days (Supplementary Fig. 2). The TGs were reflective
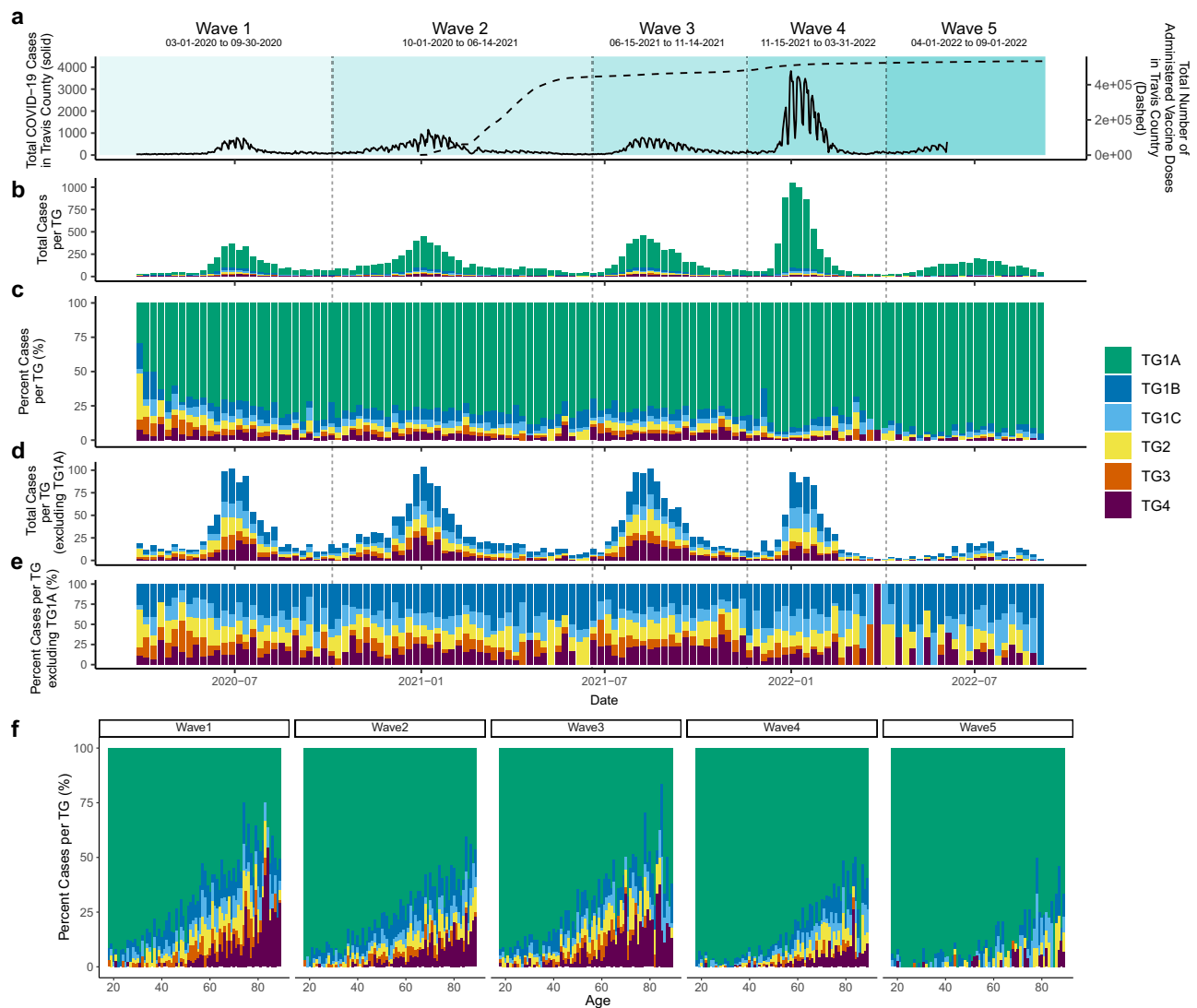
Fig. 3 | Trajectory groups over time. a Total county reported COVID-19 cases (solid line, left axis) and vaccinations (dashed line, right axis) over the cohort sampling period. Waves 1–5 are denoted with their respective boundary dates. **b** Total cases per trajectory group by week across the sampling period. **c** Relative frequency of trajectory group for each week across the sampling period. **d** Total non-TG1A cases across each week and their (**e**) relative frequency. **f** Frequency of TG per year of age for Waves 1 through 5.

of patient time to discharge, peak ordinal score, and time to peak ordinal score (Fig. 2B–D). We used the following patient classification system - TG1A: patients with mild to moderate disease who were not admitted or were quickly discharged (median discharge of 0 days); TG1B: severe patients who required a moderate length of stay (median discharge of 7 days); TG1C: severe patients with a longer hospital stay (median discharge of 11 days); TG2: critical patients who discharged by day 30 (median discharge of 16 days); TG3: critical patients who were not discharged by day 30 (with a median discharge of 39 days); TG4: all patients died within 30 days. TG1 included 91.63% of all patients, with TG1A, TG1B, and TG1C comprising 82.00%, 6.34%, and 3.29%, respectively. TG2, TG3, and TG4 represented 3.35%, 1.78%, and 3.23% of the cohort.

TGs also displayed significant association with patient demographics including sex, ethnicity, race, and age (Fig. 2E, I, Supplementary Table 1). Of note, males had worse outcomes, representing the majority of TG3 and TG4, while females had the highest representation in mild TG's. Interestingly, patients documented as Latino/Hispanic were over-represented in TG3, however this difference was not observed in other TGs. There was no significant difference in race between TGs (Supplementary Table 1, Fig. 2G). TG4 patients had the highest median age of 70, while patients in TG1A had

the lowest median age of 42 (Fig. 2H). Notably, TG1B-TG3 had similar median ages ranging from 57-61.

When comparing patient-reported SARS-CoV-2 vaccinations, the mild TG1A had higher vaccinations compared to severe/critical TGs (Supplementary Table 1). The lower severity groups TG1B and TG1C also had higher vaccination rates compared to critical groups TG2-TG4 (Supplementary Table 1).

Trajectory groups across COVID-19 waves

Based on the total COVID-19 cases in Austin's Travis County, we classified five different outbreaks (herein referred to as waves) between March 2020 to September 2022 (Fig. 3A), roughly corresponding to Alpha/Beta (waves 1–2), Delta (wave 3), and Omicron (wave 4–5) (Fig. 3A), with the total number of hospitalizations reflective of the waves (Fig. 3B).

We observed significantly higher prevalence of TG1A in waves 3, 4, and 5 compared to waves 1 and 2 (Fig. 3C, Supplementary Data 1). Additionally, despite higher total case counts during the Omicron spike (Wave 4), total severe and critical hospitalizations for TG1B-TG4 were comparable between all waves (Fig. 3D). Age-associated mortality also decreased across the waves (Fig. 3F).
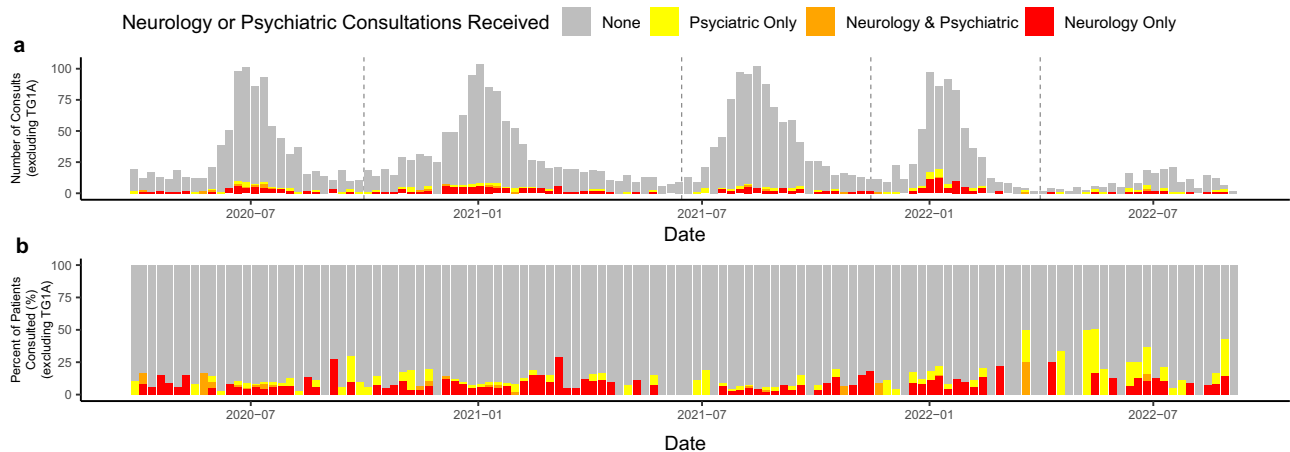
Fig. 4 | **Neurological and psychiatric consultations overtime. a** Total and (**b**) percent of COVID-19 patients receiving Neurological and/or Psychiatric consultation(s) excluding TG1A.

In waves 4–5 (Omicron), we noted a reduction in pulmonary/critical care, palliative care, infectious disease, nephrology, and neurological consultations and a decrease in diagnoses of pneumonia, acute respiratory distress, type-2 diabetes, and hypertension, (Supplementary Data 2–3) supporting the trend of a higher proportion of mild patients (TG1A) in waves 4–5. Interestingly when evaluating only the severe/critical patients (TG1B-4), neurological and psychiatric consultations remained stable across all waves, suggesting that concern of neurological involvement in severe disease remained persistent across the different circulating SARS-CoV-2 strains (Fig. 4).

Diagnoses, hospital consultations, imaging studies, and medications across trajectory groups
Diagnoses. The comparison between the fatal (TG4) and most critical TG (TG3) revealed that TG4 patients had higher rates of cardiovascular co-morbidities, such as atherosclerotic heart disease, cardiac arrest, atrial fibrillation, nicotine dependence, and long-term aspirin use (Supplementary Data 4). Additionally, chronic kidney disease, cardiac arrest and chronic obstructive pulmonary disease were also elevated, implicating multi-organ damage in fatal patients compared to critical patients. Compared to TG4, TG3 patients were more likely to be anemic and experienced more electrolyte abnormalities and mixed acid base disorders. TG3 were also more likely to have ventilator dependence, sepsis, unspecified anxiety disorder, and dysphagia.

For the less severe groups, compared to TG1B-TG1C, TG1A patients had the least co-morbid diagnoses (Supplementary Data 4). Interestingly, TG1A patients had the highest association with headache and cough. Notably, alcohol related disorders were significantly higher in TG1B and TG1C patients compared to TG1A. Further, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD), were significantly associated with TG1B-TG1C compared to TG1A. Additionally, severe/critical groups (TG1B-TG4) collectively had higher rates of several neurological and psychiatric disorders, including Alzheimer's disease, cerebral infarction, epilepsy, migraines, myoclonus, neurocognitive disorder with Lewy bodies, non-traumatic intracerebral hemorrhage, Parkinson's disease, restless leg syndrome, adjustment disorders, substance use related disorders, delirium, delusional disorders, depressive episode, generalized anxiety disorder, panic disorder, post-traumatic stress disorder, schizoaffective disorder, and schizophrenia (Fig. 5A). However, no neurological or psychiatric disorders were significantly different between the most critical TGs (TG3 vs TG2 or TG4 vs TG3).

Consultations & imaging studies
Although all consultations increased with higher TGs, TG4 received less critical care, infectious disease, gastroenterology, neurology, physical medicine and rehabilitation, hematology-oncology, psychiatry, and urology consultations compared to TG3 (Supplementary Data 5). Notably, TG3 and TG4 patients had the highest rates of palliative care and nephrology consultations, although only 64.20% of TG4 received a palliative care consult compared to TG3 (71.76%).

Notably, TG3 had the most imaging studies (Supplementary Data 6). Overall, most patients received respiratory imaging with increasing orders across TGs. Abdominal X-rays were significantly increased in more severe groups TG1B/TG1C compared to TG1A and in TG3 versus TG4. Furthermore, lower extremity venous ultrasound was also more common with increasing TG severity. Interestingly, 10.7% of the entire cohort received a Head CT without contrast, with frequency increasing from TG1A (7.6%) to TG3 (38.7%) (Fig. 5, Supplementary Data 6).

Medication administration
The least medication administration was in TG1A, likely due to fastest discharge (Supplementary Data 7). Notably, dexamethasone usage was not different between TG3/TG4, while Remdesivir was higher in TG3. Higher medication usage in TG4 compared to TG3 included haloperidol, morphine, lorazepam, scopolamine, glycopyrrolate, which are often administered with comfort-care measures, in line with higher palliative care consultations and 'do-not-resuscitate' orders in TG4. Additionally, neuromuscular blockers, atracurium, rocuronium, and succinylcholine as well as fentanyl, etomidate, and propofol were used more often in TG3 than TG4, correlating with a higher proportion of mechanical ventilation.

Laboratory tests and vital signs
Several laboratory tests demonstrated significant separation of TGs at admission and through hospitalization (Fig. 5B–G). Interestingly, albumin was one of the best predictors of disease severity, displaying the most ordinal relationship across TGs, both at admission and throughout hospitalization (Fig. 4C, Supplementary Data 8), with lower values in the more severe TGs, in correspondence with higher malnutrition diagnosis in the critical TG3. On admission (day 0-1), several other predictive labs distinguished the mild TG1A group from the more severe groups. TG1A had higher red blood cell count, hematocrit, and hemoglobin compared with more severe TGs (Supplementary Fig. 3). In addition, TG1A had elevated absolute basophils, eosinophils, lymphocytes, lower absolute neutrophils and immature granulocytes compared to more severe TGs and lower D-Dimer, sedimentation rate, lactate, C reactive protein and fibrinogen as well as higher calcium compared to the more severe TGs (Supplementary Data 8 and 10). Furthermore, in comparing the critical and fatal TGs, TG4 had elevated AST, total bilirubin, creatinine, BUN and anion gap (AGAP), and lower total
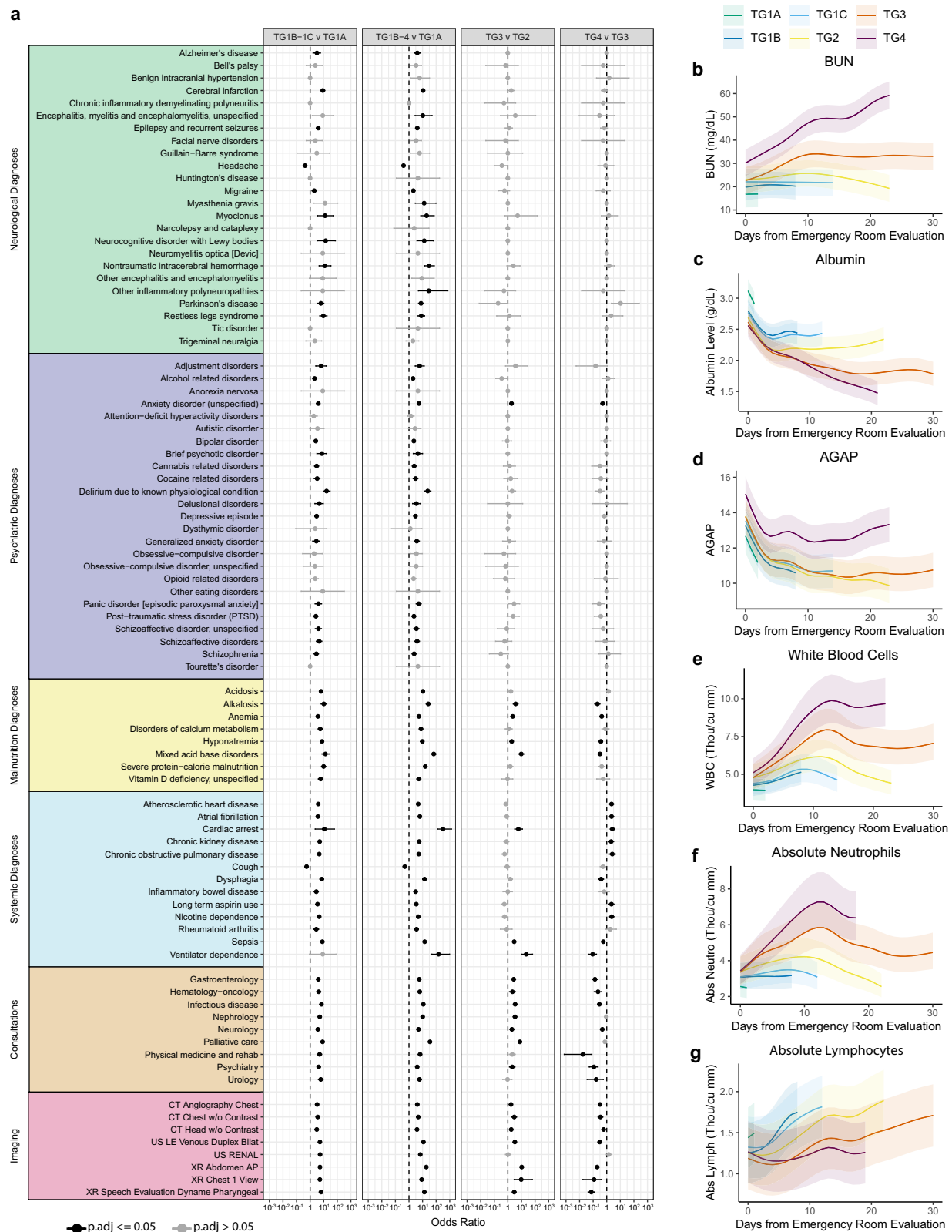
Fig. 5 | Diagnosis, consultation, and imaging differences between COVID-19 TGs. a Odds ratios of key diagnoses, consultations, and imaging between TGs. Error bars denote 95% confidence interval. Longitudinal modeling of laboratory testing over 30 days of hospitalization by TG for (**b**) Blood Urea Nitrogen (BUN), **c** Albumin, **d** Anion Gap (AGAP), **e** White Blood Cells, **f** Absolute Neutrophils, **g** Absolute Lymphocytes with 95% Confidence interval denoted as shaded region. Laboratory testing modeling results by TG were trimmed to days with data for greater than 10% of the TG. Total subjects for each TG are as follows: TG1A $n = 17476$, TG1B $n = 1351$, TG1C $n = 701$, TG2 $n = 715$, TG3 $n = 380$, TG4 $n = 689$.

protein and CO2. Finally, the fatal TG4 had higher lactate, AGAP and lower arterial pH compared to critical TG3.

Vitals signs from the first two days were averaged for each patient to identify changes across TG (Supplementary Data 9 and 11). Notably, systolic and diastolic blood pressure and oxygen saturation decreased with severity along with higher respiratory rate and lower Glasgow coma scores (GCS). However, only GCS was significantly different between TG4 and TG3. Over hospitalization, TG3/TG4 continued to have abnormalities in oxygen saturation, respiratory rate, and GCS to day 30 (Supplementary Fig. 4).

Discussion

We present a comprehensive evaluation of a large retrospective cohort of COVID-19 patients from five Central Texas hospitals across SARS-CoV-2 waves between March 2020 and September 2022. We identified six distinct clinical trajectories that distinguished COVID-19 patient outcomes and provide a detailed analysis of risk factors and clinical features of COVID-19 disease severity in acute care patients. Interestingly, despite known prevalence of cardiopulmonary complications in COVID19 patients, our analysis reveals a multi-system failure in severe COVID-19 with a high association with neuropsychiatric co-morbidities and malnutrition.

Our cohort was similar to other studies in terms of median age and sex distribution[3,18,19]. The overall 30-day mortality rate was 3.23%, with admitted patients at 7.73% and severe/critical TGs at 17.96%, in line with reported 11–23% rates[20–22]. Similarly to other studies[18,19], we identified older age as a mortality risk factor, while younger age was associated with faster hospital discharge. Interestingly, the median age was similar between non-fatal severe/critical groups, suggesting that age may be a coarse risk factor for disease severity. Furthermore, males were over-represented in the most critical TGs (TG3/TG4), in line with sex as a risk factor of COVID-19 severity[3,7,23]. Additionally, our results support Hispanic ethnicity correlating with severity[24,25]. Notably, Hispanics formed a higher percentage of TG3, with higher rates of obesity and cardiovascular/renal comorbidities. This suggests that differences in outcomes among Hispanic patients may be associated with pre-existing chronic conditions, although some studies have attributed these disparities to delayed clinical presentation with more advanced disease[26].

Over 2.5 years, there was a reduction in severe/critical cases within later COVID-19 waves. This reduction may be due to increased vaccinations by the end of Wave 2, less severe strains (Omicron), increasing immunity from previous infections, or increasing incidental hospital COVID-19 diagnoses. Vaccinations were most prevalent in TG1A patients, demonstrating the protective benefit against severe disease and mortality[27]. However, further research is needed to ascertain whether vaccinations or less severe strains may account for lower severity with later waves[28,29].

We observed a high frequency of neuropsychiatric diagnoses, including anxiety, depression, bipolar disorder, encephalopathy, dementia, and seizures and higher rates of central nervous system imaging in association with severe COVID-19 trajectories. These findings are in line with other studies finding higher neuropsychiatric complications in severe COVID-19[30]. Despite the increase in case numbers in wave 4 (corresponding to the Omicron SARS-CoV-2 variant), the relative proportion of severe/critical COVID-19 patients receiving neurological and psychiatric consultations remained constant, indicating that neuropsychiatric complications persisted across different SARS-CoV-2 strains and did not abate with milder variants. Interestingly, the presence of neuropsychiatric diagnoses did not differentiate patients between critical trajectory groups (TG3 vs TG2 and TG4 vs TG3), suggesting that these diagnoses may have a lesser impact on COVID-19 related mortality compared to systemic diagnoses such as cardiac and respiratory complications. Nevertheless, TG3 patients were more likely to have brain imaging than TG2 patients, suggesting that concern of neurological complications remained high for patients with more severe COVID-19. Importantly, the observed higher association with neuropsychiatric complications in severe COVID-19 may inform the persistence of neuropsychiatric sequelae in Long-COVID patients following acute SARS-CoV-2 infection[31–33].

One of the best severity-predictive lab markers at admission and throughout hospitalization was albumin, with the lowest level in TG4 and highest in TG1A in alignment with previous studies[34–36]. Although hypoalbuminemia is known to be a marker of infection, inflammation, acute and chronic illness[35], likely due to reduced liver synthesis, increased catabolism, or vascular permeability[37], albumin is not part of current COVID-19 risk-stratification algorithms. Based on our data, the inclusion of albumin in risk assessment could greatly improve prediction accuracy of COVID-19 outcomes.

Additionally, while not the best marker of nutritional status[38], in association with higher malnutrition codes in severe/fatal patients, low albumin points to nutritional insufficiency as another key component in COVID-19 outcomes. Notably, other nutritional components, e.g. thiamine, Vitamin D, and B vitamins, which are also vital for neurological health, were not routinely checked in most patients, and multivitamins were administered to at most 20% of any TG, and only 10% of fatal patients. Our findings highlight the complex interaction between nutritional status and inflammation that is reflected by low albumin levels in severe patients and raises the question of whether evaluation of micronutrients, such as albumin, pre-albumin, thiamine, Vitamin D, and B vitamins, at initial clinical presentation in acute care patients, may help identify vulnerable patients, as well as whether measurement and replacement of micronutrients may benefit patient outcomes.

Furthermore, hypoalbuminemia may contribute to the neurological co-morbidities observed in our study, given albumin's documented neuroprotective effects, modulation of neuronal and glial cell signaling and antioxidant properties[39,40]. For example, albumin's anti-inflammatory and antioxidant properties protect endothelial cells, potentially reducing cerebral atherosclerosis[41–43]. Its anticoagulant effects, through inhibition of arachidonic acid oxidation and thromboxane A2 synthesis, may lower stroke risk[44]. In Alzheimer's disease, albumin has been shown to suppresses amyloid-beta protein formation and accumulation[45], while in Parkinson's disease, it slows α-synuclein aggregation[46] and is associated with better cognitive function, lower motor impairment, and decreased mortality risk[47].

Immunologically, our results support association of high neutrophils and immature granulocytes and low lymphocytes and monocytes in severe patients[48]. Notably, we did not observe a significant difference between TG3 and TG4 at admission, suggesting that these immune markers are reflective of only severity and not mortality. Interestingly, changes in immune gene expression and proteomics are associated with both COVID-19 severity and mortality[49,50], suggesting that additional immune markers may offer more accurate prognosis of COVID-19 outcomes.

We also observed higher rates of sepsis, shock, and immunodeficiency in critical patients, with RA and IBD over-represented in critical TGs, supporting evidence that certain immune conditions may predispose to more severe COVID-19[51]. The risk of increased COVID-19 severity for immunodeficient and immunosuppressed patients has been observed previously[52–55]. For example, immunosuppressed solid organ transplant recipients mount slower antibody responses resulting in prolonged SARS-CoV-2 nasal viral loads and innate inflammation[56] contributing to their greater risk of severe disease. However, for autoimmune diseases the degree of immunosuppression greatly varies, with some diseases such as RA[57] and IBD[58,59] associating with more severe disease and others such as multiple sclerosis often experiencing better COVID-19 outcomes[60–62]. Thus, the risk that immunodeficiency and immunosuppression pose can differ between immune diseases.

Acid-base dysregulation was another set of diagnoses enriched in severe TGs. Notably, anion gap, a measure of acid-base homeostasis, increased in severe TGs in association with low albumin. This relationship is significant as albumin plays a crucial role in maintaining acid-base balance due to its buffering capacity[63]. The high anion gap may be explained by decline in renal function or higher levels of sepsis contributing to lactic acidosis in severe patients[64]. Importantly, renal dysfunction can exacerbate

both hypoalbuminemia[65] and acid-base dysregulation[66], potentially creating a detrimental cycle. The kidneys' role in acid-base homeostasis through bicarbonate reabsorption and acid excretion is compromised in patients with impaired renal function, further contributing to metabolic acidosis and increased anion gap[67]. Physiologically, acid-base dysregulation can lead to abnormalities across multiple organs but notably within the cardiovascular system[68]. Indeed, cardiac dysfunction increased across severe/critical TGs, with highest rates in the fatal TG4. Given more severe outcomes in patients with acid-base disorders, it is critical for physicians to promptly identify and correct acid-base dysregulation causes, while also addressing related factors such as hypoalbuminemia and renal dysfunction, toward improving COVID-19 outcomes.

There were several limitations to our study. First, our cohort was from a single health system and was disproportionately Hispanic and white. Second, all data were retrieved from EHRs, known to have missing data and lower quality data with respect to demographics, e.g. race and ethnicity[69]. Also, our clinical dataset did not include viral load or SARS-CoV-2 variant information, though we were able to use epidemiological data to estimate the prevalence of strains over time.

In conclusion, our identified clinical signatures could help clinicians better predict disease trajectories in acute COVID-19 and anticipate elevation of care versus discharge. Importantly, we highlight an association between COVID-19 severity and neuropsychiatric complications as well as nutritional insufficiency as key risk factors for COVID-19 outcomes, raising the urgency for prompt evaluation and treatment of these conditions toward improving patient outcomes in the ED, hospital and post discharge.

Data availability

Deidentified raw data will be made available upon reasonable request to the corresponding author of this manuscript. The raw data is not made readily available to protect patient health information, but source data for all figures are provided in Supplementary Data 1-12.

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Author contributions

C.M. and E.M. conceived this work. C.M., E.S., and N.B. conceived the methodology and software. C.M., E.S., and N.B. undertook the formal analysis. C.M., E.S., N.B., and J.M. obtained resources and data curation. C.M. and E.S. was responsible for visualization. E.M. obtained funding. E.M., J.R., and C.M. conducted the project administration. E.M., J.R., D.W. were responsible for supervision. C.M. and E.M. wrote the original draft. C.M., E.S., N.B., J.M., R.M., D.W., J.B., W.M.B, and E.M. reviewed and edited the final manuscript.

Competing interests

C.M., E.S., N.B., J.M., R.M., D.W., and J.R. have no disclosures. J.B. has given a talk on updates in Hospital Medicine 8/04/2023 at the 11th Management of the Complex Hospitalized Patient. W.M.B. has received honoraria for COVID-19 and Long COVID lecture to the HNI institute, TNP Nurse Practitioners conference, travel support for Texas ACP conference and Society of Hospital Medicine national conference for Long COVID presentations. E.M. has received honoraria for COVD-19 and Long COVID work from National Center for Health Research and American Academy of Physical Medicine and Rehabilitation.

Additional information

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