

Comparing Clinical Characteristics of Influenza and Common Coronavirus Infections Using Electronic Health Records

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Background. We compared outcomes in inpatients and outpatients, pre-COVID-19, who were infected with either coronavirus or influenza.

Methods. Using deidentified electronic health records data from the Geisinger-Regeneron partnership, we compared patients with RT-PCR–positive tests for the 4 common coronaviruses (229E, HKU1, NL63, OC43) or influenza (A and B) from June 2016 to February 2019.

Results. Overall, 52 833 patients were tested for coronaviruses and influenza. For patients ≥ 21 years old, 1555 and 3991 patient encounters had confirmed positive coronavirus and influenza tests, respectively. Both groups had similar intensive care unit (ICU) admission rates (7.2% vs 6.1%, $P = .12$), although patients with coronavirus had significantly more pneumonia (15% vs 7.4%, $P < .001$) and higher death rate within 30 days (4.9% vs 3.0%, $P < .001$). After controlling for other covariates, coronavirus infection still had a higher risk of death and pneumonia than influenza (odds ratio, 1.64 and 2.05, $P < .001$), with no significant difference in ICU admission rates.

Conclusions. Common coronaviruses cause significant morbidity, with potentially worse outcomes than influenza. Identifying a subset of patients who are more susceptible to poor outcomes from common coronavirus infections may help plan clinical interventions in patients with suspected infections.

Keywords. common coronavirus; influenza; electronic health records; epidemiology.

The coronavirus disease 2019 (COVID-19) pandemic not only focused attention on the unique and devastating impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, but also focused attention on the role of coronaviruses in public health. While previous epidemic coronaviruses, such as SARS (severe acute respiratory syndrome) and MERS (middle east respiratory syndrome), were relatively contained, the massive impact of SARS-CoV-2 infections emphasizes the need for more knowledge of all strains of coronaviruses. During a typical respiratory disease season, millions of people across the globe are infected by influenza and common coronaviruses. However, in the absence of widespread infections like the current pandemic, the treatment of most people with flu-like symptoms is mainly based on clinical diagnosis and not based on laboratory results. In some reports, common coronaviruses account for 20% of upper respiratory

infections in adults [1]. Considering the similar clinical presentations of all upper respiratory viral infections, it is often hard to distinguish them clinically [2]. Although common coronavirus species (229E, HKU1, NL63, and OC43) do not behave exactly like the novel coronavirus COVID-19, comparing coronavirus and influenza is timely, given the increased attention and public health consequences of current outbreaks [3, 4].

Common coronavirus infection generally manifests as a mild flu-like syndrome but may lead to lower respiratory tract infections in children, the elderly, or patients with certain chronic conditions [5]. Of the common species, 229E and OC43 rarely infect the lower respiratory tract, so NL63 and HKU1 are thought to be more likely than those other species to cause severe lower respiratory infections [6]. Epidemiologic studies investigating upper and lower respiratory infections report varying results depending on both geography and patient populations. For example, a surveillance study in Michigan showed higher odds of severe infections in children with 229E and lower odds of severe infection with NL63 [7].

In the United States, while most common coronavirus infections are in adults and peak in early winter, the age distribution by species differs [8]. For example, infections with 229E are less common in children than those of the 3 other species [8]. Interestingly, in a pediatric cohort from Norway,

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33% of asymptomatic control children were infected with NL63 or HKU1 versus 22% in the symptomatic hospitalized cohort [9]. A small Spanish cohort showed that adults with common coronavirus were mainly male smokers, presented mainly with nonspecific influenza-like illness symptoms or pneumonia, and generally had favorable outcomes despite a 52% hospitalization rate [10]. Specific coronavirus species have been implicated in outbreaks of severe infection in a neonatal intensive care unit (ICU; 229E) and in a long-term care facility (NL63) [1].

In comparing influenza versus coronavirus infections, a prospective cohort of viral pneumonia patients admitted to Italian ICUs showed a 15-times higher infection rate of influenza than common coronavirus [11]. A pediatric cohort from Korea collected in the fall of 2014 showed higher rates of coronavirus infections, as well as a significant rate of lower respiratory tract infections [12]. A prospective observational study of adults presenting with influenza-like illness who were tested for respiratory viral infection showed similar outcomes for death, pneumonia, and ICU admission for patients with influenza compared to those infected with other respiratory viruses [2]. In the same cohort, patients with no respiratory virus reported after testing had similar rates of death and ICU admission but a lower rate of pneumonia.

At the beginning of the COVID-19 pandemic, we investigated outcomes in adult inpatients and outpatients with reverse transcription polymerase chain reaction (RT-PCR)-confirmed cases of common coronaviruses and compared them to those with laboratory-confirmed cases of influenza to explore whether or not the results of the study could help better understanding of SARS-CoV-2 infections. The increased use of RT-PCR as a gold standard for diagnosing influenza and coronavirus, and the availability of electronic health records (EHRs) at the Geisinger Health System, Regeneron's partner in the DiscovEHR program, make it possible to compare the clinical characteristics of these 2 virus infections in a large number of patients. The DiscovEHR program is a partnership between the Regeneron Genetics Center (RGC) and Geisinger Healthcare, a large integrated delivery network in Pennsylvania and New Jersey, whose goal is to advance precision medicine. In the partnership, the RGC provides exome sequencing to participants in Geisinger's MyCode program, and Geisinger provides deidentified EHR data to the RGC [13].

METHODS

We extracted a single cohort from records of adult (≥ 21 years old) patients with RT-PCR-positive tests for influenza A, B, or one of the common coronaviruses (229E, HKU1, NL63, and OC43). The cohort was later substratified into inpatient and outpatients, each categorizing patients with either coronavirus or influenza virus. Multiplex RT-PCR-based testing was part of a large respiratory pathogen panel (termed here the respiratory

panel) that tests for 17–21 respiratory pathogens (viral and bacterial) at once (BioFire Filmarray; BioFire). Additional testing included outpatient testing (the targeted test) performed by GeneXpert RT-PCR assay targeting influenza and respiratory syncytial virus (Cepheid). Specifically, for patients presenting with respiratory signs or symptoms, the respiratory panel was administered in patients who (1) were being admitted to the hospital; (2) were being admitted to an observation unit; or (3) were members of groups at high risk for complications from influenza infection [14]. Low-risk outpatients and emergency department patients who were not being admitted received the targeted test.

We analyzed data in our local, deidentified instance of data extracted from Geisinger's EHR system. The data for this analysis spanned the period from late June 2016 to late February of 2019. Although the data in the EHR dataset is date-shifted due to deidentification, it preserves seasonality. We identified comorbidities using the International Classification of Diseases (ICD)-10-CM codes listed in the footnote in Table 1. Because of reports of the contribution of comorbidities like obesity (defined as BMI ≥ 30 in this study), hypertension, and diabetes to poor outcomes in patients with COVID-19 [15], we created categorical variables that combined the risk factors (obesity and hypertension; obesity and diabetes; obesity, diabetes, and hypertension). We used existing flags in the EHR dataset to identify ICU admissions, and mortality data to identify deaths within 30 days of diagnosis. Of note, because patients could have tests performed on different visits, we performed our analysis on the encounter level; therefore, patients may be represented in more than one encounter.

Due to the likely differences in severity between people tested in the inpatient versus outpatient settings, we performed our bivariate analyses for (1) the overall (inpatients and outpatients combined) cohort, and (2) the separate outpatient and inpatient cohorts. Multivariate logistic regression was performed for all the cohorts, but only results for the overall cohort were reported.

Although the study focused on outcomes for patients who were tested using the respiratory panel, we also analyzed data from the influenza outpatient testing program, which included a large number of tests for influenza A and B RNA in nasal swabs, nasopharyngeal swabs and unspecified respiratory specimens, all of which were identified by their Logical Observation Identifiers Names and Codes (LOINC) identifiers. Additional influenza testing was included to provide broader epidemiologic context to the results, but the final analysis was limited to the high-risk patients who were tested using the respiratory panel.

To summarize, the main cohorts analyzed were:

- All adult patients with either coronavirus or influenza detected on respiratory panel

Table 1. Comparison Between Patients Infected With Coronavirus and Those With Influenza

Factor	Coronavirus	Influenza	PValue
n	1555	3991	
Age at diagnosis, y, median (IQR)	61.5 (44.2–75.0)	62.6 (45.5–76.2)	.20
Age > 65 y	677 (43.5)	1832 (45.9)	.11
Diagnosis quarter			
1	1119 (72.0)	2991 (74.9)	<.001
2	87 (5.6)	481 (12.1)	
3	24 (1.5)	18 (0.5)	
4	325 (20.9)	501 (12.6)	
Male	641 (41.2)	1719 (43.1)	.21
Race, white	1467 (94.3)	3814 (95.6)	.055
ICU service	112 (7.2)	242 (6.1)	.12
Pneumonia	234 (15.0)	297 (7.4)	<.001
CHD	202 (13.0)	476 (11.9)	.28
CKD	203 (13.1)	435 (10.9)	.024
CLD	494 (31.8)	1009 (25.3)	<.001
T2D	231 (14.9)	629 (15.8)	.40
Death within 30 days	76 (4.9)	118 (3.0)	<.001
Coronavirus ICD-10	101 (6.5)	0 (0.0)	<.001
Influenza ICD-10	13 (0.8)	2184 (54.7)	<.001
HTN	242 (15.6)	757 (19.0)	.003
Inpatient	675 (43.4)	1534 (38.4)	<.001
Smoking	951 (61.8)	2180 (55.0)	<.001
ARDS	2 (0.1)	14 (0.4)	.26
Obesity	725 (48.0)	1773 (46.3)	.25
Obesity HTN	118 (7.8)	369 (9.6)	.038
Obesity T2D	144 (9.5)	401 (10.5)	.31
Obesity HTN T2D	33 (2.2)	134 (3.5)	.013

Data are No. (%) except where indicated.

Abbreviations: ARDS, acute respiratory distress syndrome; CHD, chronic ischemic heart disease (ICD-10-CM I25.*); CKD, chronic kidney disease (ICD-10-CM N18.*); CLD, chronic lung disease (ICD-10-CM J40.*–J47.*); HTN, essential hypertension (ICD-10-CM I10.*); ICD, International Classification of Diseases; IQR, interquartile range; T2D, type 2 diabetes (ICD-10-CM E11.*).

- All adult patients with either coronavirus or influenza detected on respiratory panel, with outpatients and inpatients analyzed separately.

The supplementary cohorts were:

- All patients with either coronavirus or influenza detected on respiratory panel and all patients with positive RT-PCR for influenza on other tests
- All pediatric patients with either coronavirus or influenza detected on respiratory panel.

In the bivariate analysis, results were expressed as a mean with a corresponding standard deviation (SD), or as a median with a corresponding interquartile range (IQR) for continuous variables. Results were described as proportions, n (%), for categorical variables. Continuous variables were compared with Student *t* test or Mann-Whitney *U* (Wilcoxon rank sum) test as appropriate; categorical variables were compared by χ^2 tests or Fisher exact test as appropriate. In multivariate logistic regressions, 3 clinical outcomes were tested against predictors: death within 30 days of diagnosis, treatment by the critical care service

(ICU), and infectious pneumonia. $P < .05$ was considered statistically significant. Statistical analysis was performed using R software version 4.0.0 (R Foundation for Statistical Computing; <https://www.R-project.org/>) and Stata release 14 (StataCorp LP). We performed this study using deidentified data under the terms of the Regeneron-Geisinger collaboration, which is approved by Geisinger's institutional review board.

RESULTS

Overall Cohort

Overall, out of 52 833 total patients tested with the respiratory panel, for patients ≥ 21 years old, 1555 and 3991 patient encounters had positive molecular test results for coronavirus or influenza, respectively. Eighty encounters in which patients tested positive for both viruses were excluded (Table 1). Both cohorts were similar in terms of age and sex. Although over 70% of both coronavirus and influenza infections occurred in the first quarter of the year, more coronavirus infections than influenza infections occurred in the fourth quarter of the year. The seasonality patterns of both types of viruses are reported in Figure 1. Among all the positive coronavirus tests, more came from the inpatient setting, as expected due to compliance with

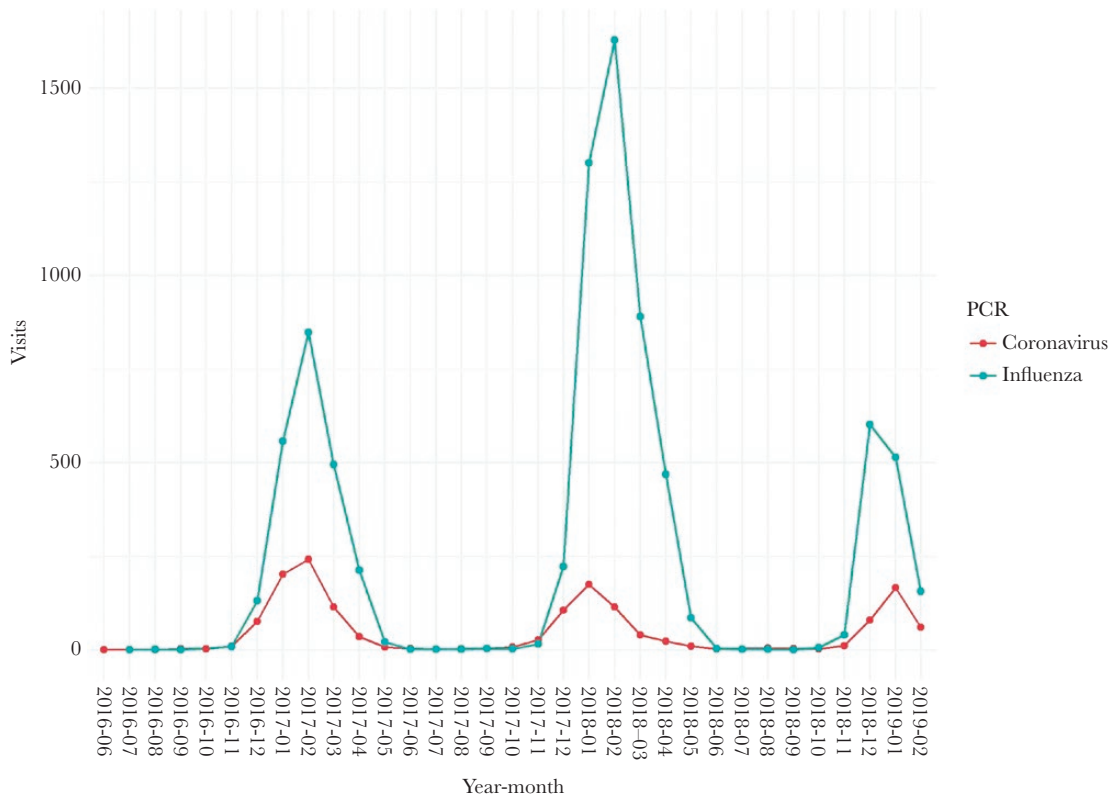


Figure 1. Seasonality of influenza and coronavirus at Geisinger Healthcare. Abbreviation: PCR, polymerase chain reaction.

the previously described standard of care practices testing outpatients for influenza virus within the Geisinger system (43.4% vs 38.4%, $P < .001$). In terms of clinical documentation, only 6.5% of RT-PCR-positive coronavirus patients had the corresponding ICD-10 code on their chart (B34.2), while 54.7% of influenza patients had codes J09–J11 on their medical record.

Of the measured comorbidities among patients with coronavirus and influenza virus respectively, rates of chronic ischemic heart disease (13.0% vs 11.9%, $P = .28$), type 2 diabetes (14.9% vs 15.8%, $P = .4$), obesity (48.0% vs 46.3%, $P = .25$), and obesity with type 2 diabetes (9.5% vs 10.5%, $P = .31$) were similar among both groups; rates of chronic kidney disease (13.1% vs 10.9%, $P = .024$), chronic lung disease (31.8% vs 25.3%, $P < .001$), and smoking (61.8% vs 55%, $P < .001$) were higher in the coronavirus group; and the prevalences of hypertension (15.6% vs 19.0%, $P = .003$), obesity with hypertension (7.8% vs 9.6%, $P = .038$), and obesity with both hypertension and diabetes (2.2% vs 3.5%, $P = .013$) were higher in the influenza group. In terms of outcomes, rates of ICU admission were slightly higher in the coronavirus group, although not statistically significant (7.2% vs 6.1%, $P = .12$), but the rate of pneumonia was twice as high in the coronavirus group (15% vs 7.4%, $P < .001$). The coronavirus group also had a significantly higher death rate within 30 days (4.9% vs 3%, $P < .001$). There was no significant difference in rates of acute respiratory distress syndrome (ARDS; 0.1% vs 0.4%, $P = .26$) between these two groups.

In multivariate logistic regression (Figure 2) for the full cohort, after controlling or adjusting for other predictors, coronavirus infection was still related to higher risk of death (odds ratio [OR], 1.64, $P < .001$) and infectious pneumonia (OR, 2.05, $P < .001$) than influenza. Consistent with bivariate analysis, coronavirus was not an independent predictor (OR, 0.80, $P = .337$) of ICU service. Other independent predictors of death within 30 days included age (OR, 3.56, $P < .001$), chronic ischemic heart disease (OR, 0.51, $P = .009$), chronic lung disease (OR, 0.56, $P = .005$), hospital admission (OR, 8.64, $P < .001$), and ICU service (OR, 5.66, $P < .001$). Other independent predictors of pneumonia included age (OR, 1.30, $P = .017$), sex (OR, 1.30, $P = .009$), chronic ischemic heart disease (OR, 0.66, $P = .004$), chronic lung disease (OR, 1.31, $P = .012$), and hospital admission (OR, 6.33, $P < .001$). Sex (OR, 1.34, $P = .013$), smoking (OR, 1.56, $P = .001$), type 2 diabetes (OR, 0.57, $P = .049$), and pneumonia (OR, 5.50, $P < .001$) were the independent predictors of ICU service.

Separate Outpatient and Inpatient Cohort Results

In the outpatient setting, 880 and 2457 patient encounters had positive tests for coronavirus or influenza, respectively (Table 2). In this subgroup, the comorbidities followed the same pattern as the overall group, and there were no statistically significant differences in terms of clinical outcomes (pneumonia, death within 30 days, ICU admission). For

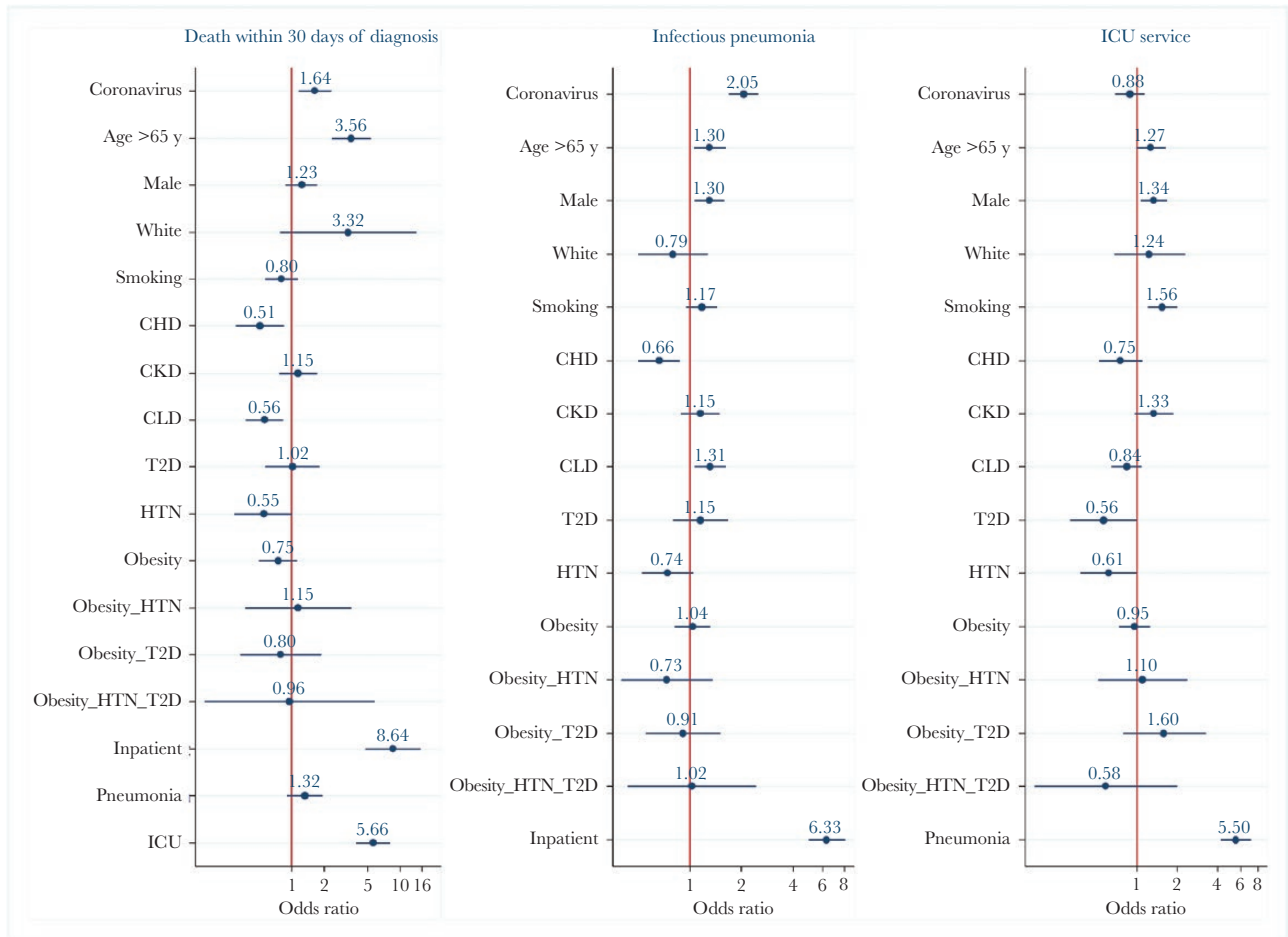


Figure 2. Multivariate analysis—full cohort. Abbreviations: CHD, chronic ischemic heart disease; CKD, chronic kidney disease; CLD, chronic lung disease; HTN, essential hypertension; ICU, intensive care unit; T2D, type 2 diabetes.

inpatients, 675 and 1534 patients tested positive for coronavirus or influenza, respectively (Table 2). The inpatient populations were more similar than the overall group in terms of comorbidities, with only a statistically significant difference in smoking (68.9% vs 61.3%, $P < .001$) in the coronavirus group. Of note, the combined inpatients and outpatient coronavirus group was younger than the influenza group (average age 69.7 vs 72 years, $P < .001$), and there were more white patients in the influenza group (97.2% vs 95.6%, $P = .047$). In the combined subgroup, there was no significant difference in ICU admission rates (16.4% vs 15.8%, $P = .69$); however, the coronavirus group had higher rates of pneumonia (30.4% vs 14.5%, $P < .001$) and death within 30 days (10.5% vs 6.7%, $P = .002$). Of note, the influenza group had a statistically significant higher rate of ARDS; however, the overall rate was very low in both groups and the clinical difference may not be especially relevant (0.1% vs 0.9%, $P = .049$).

Supplementary Analysis

While we focused on adult patients, results for children (<21 years old) are available in Supplementary Table 1. Of note,

results were similar across age groups. We also compared results from patients who were tested with respiratory panels versus those who received other molecular tests in the same time period. Approximately 97% of patients who received the other tests were outpatients, and 32% of those tests were positive for one of the viruses (influenza A, B, or respiratory syncytial virus). For patients tested with the full respiratory panel, 9.3% were positive for influenza, and 4.3% were positive for coronavirus. Outpatients who tested positive in the respiratory panel had a subsequent 7-day admission rate that was 5 times higher than those who received other outpatient molecular tests (3% vs 0.6%, $P < .001$), as may be expected with only high-risk outpatients tested with the full respiratory panel.

DISCUSSION

This retrospective, observational study provided data that allow for a detailed comparison of patients infected with common coronavirus or influenza. We chose to focus on adults because most studies on coronaviruses focus on pediatric populations, and thus results in an adult population are a

Table 2. Comparison Between Patients Infected With Coronavirus and Those With Influenza, by Setting

Factor	Outpatients Only			Inpatients Only		
	Coronavirus	Influenza	PValue	Coronavirus	Influenza	PValue
n	880	2457		675	1534	
Age at diagnosis, y, median (IQR)	54.3 (36.6–68.4)	54.2 (36.9–70.0)	.48	69.7 (57.6–80.6)	72.0 (60.9–82.6)	<.001
Age > 65 y	271 (30.8)	804 (32.7)	.29	406 (60.1)	1028 (67.0)	.002
Diagnosis quarter						
1	642 (73.0)	1848 (75.2)	<.001	477 (70.7)	1143 (74.5)	<.001
2	35 (4.0)	267 (10.9)		52 (7.7)	214 (14.0)	
3	11 (1.3)	12 (0.5)		13 (1.9)	6 (0.4)	
4	192 (21.8)	330 (13.4)		133 (19.7)	171 (11.1)	
Male	306 (34.8)	999 (40.7)	.002	335 (49.6)	720 (46.9)	.24
Race, white	822 (93.4)	2323 (94.5)	.21	645 (95.6)	1491 (97.2)	.047
ICU service	1 (0.1)	0 (0.0)	.26	111 (16.4)	242 (15.8)	.69
Pneumonia	29 (3.3)	75 (3.1)	.72	205 (30.4)	222 (14.5)	<.001
CHD	70 (8.0)	170 (6.9)	.31	132 (19.6)	306 (19.9)	.83
CKD	49 (5.6)	98 (4.0)	.050	154 (22.8)	337 (22.0)	.66
CLD	223 (25.3)	456 (18.6)	<.001	271 (40.1)	553 (36.0)	.067
T2D	88 (10.0)	249 (10.1)	.91	143 (21.2)	380 (24.8)	.068
Death within 30 days	5 (0.6)	15 (0.6)	1.00	71 (10.5)	103 (6.7)	.002
Coronavirus ICD-10	40 (4.5)	0 (0.0)	<.001	61 (9.0)	0 (0.0)	<.001
Influenza ICD-10	10 (1.1)	899 (36.6)	<.001	3 (0.4)	1285 (83.8)	<.001
HTN	104 (11.8)	389 (15.8)	.004	138 (20.4)	368 (24.0)	.068
Smoking	493 (56.3)	1247 (51.1)	.008	458 (68.9)	933 (61.3)	<.001
ARDS	1 (0.1)	0 (0.0)	.26	1 (0.1)	14 (0.9)	.049
Obesity	448 (53.3)	1094 (47.4)	.004	277 (41.4)	679 (44.5)	.18
Obesity HTN	59 (7.0)	213 (9.2)	.050	59 (8.8)	156 (10.2)	.31
Obesity T2D	57 (6.8)	165 (7.2)	.71	87 (13.0)	236 (15.5)	.13
Obesity HTN T2D	14 (1.7)	76 (3.3)	.015	19 (2.8)	58 (3.8)	.26

Data are No. (%) except where indicated.

Abbreviations: ARDS, acute respiratory distress syndrome; CHD, chronic ischemic heart disease (ICD-10-CM I25.*); CKD, chronic kidney disease (ICD-10-CM N18.*); CLD, chronic lung disease (ICD-10-CM J40.*–J47.*); HTN, essential hypertension (ICD-10-CM I10.*); ICD, International Classification of Diseases; IQR, interquartile range; T2D, type 2 diabetes (ICD-10-CM E11.*).

more novel contribution to the literature. Additionally, as seen in [Supplementary Table 1](#), results in children generally mirrored results in the adult population. Because these are observational data, it is possible that the different viruses were not the causal reason for worse outcomes (death and pneumonia), but just correlated with other events that may have led to these outcomes. The level of detail of the dataset, the comparable populations, and the results of our analysis when controlled for covariates as well as different clinical settings strengthen the causal role of the viruses rather than different populations in the outcomes.

While studies have shown that about half of patients admitted to the ICU with severe respiratory disease are positive for a respiratory virus [11], our study, reflective of only 2 virus groups, shows that the converse, as expected, is not true; only approximately 6.5% of patients with coronavirus or influenza infections require an ICU admission. Although much lower than ICU admission rates for community-acquired pneumonia (23%) [16], viral respiratory infections are still an important cause of morbidity.

The lack of correlation between RT-PCR results and ICD codes is an important issue for epidemiologic or claims-based

studies, many of which are based on diagnosis codes only. It is not known, but is assumed, that this finding is generalizable to a larger subset of hospitals. Because treatment for most patients with viral infections is supportive, RT-PCR testing may not be seen as valuable for clinical decision making; however, these results highlight the potential importance of knowing the patient's respiratory virus status. Results have an impact for inpatient and outpatient antiviral stewardship, under the premises of precision medicine, that is not using antiviral medication unless influenza is documented. Reports from Geisinger have shown that testing ICU patients for respiratory viruses is associated with lower mortality and costs for ICU inpatient stays [17]. Additionally, because viral infections are often nonspecific in their presentation, clinicians are unable to distinguish between coronavirus, which does not benefit from oseltamivir therapy, or influenza, which can benefit. Our results, which grouped all common coronaviruses, rather than separating results by species, may not be generalizable to other time periods because of the predominance of different species during different years or in different geographies. A broader investigation may include substratification of coronavirus subtypes and influenza strains and a lookback to data originating prior to 2016.

Focusing on patients with more severe disease, as depicted in the inpatient subgroup results in this study, provides information for cases where clinical decision-making can be more challenging and where the risk of poor outcomes is inherently higher. For example, the much higher subsequent admission rate shows that the tested population was sicker than the overall surveillance population. In terms of outcomes, only data recorded in the EHR were captured, so some patient deaths may have been missed. Geisinger's patient population is relatively stable and constrained, so there are probably fewer missing data in this cohort than in a system with multiple health systems.

Planned future work in the Regeneron Genetic Center involves analyzing host genetic features in addition to clinical variables to better understand their effects on outcomes. With a larger patient population, we will also have enough power to analyze outcomes by viral subtype.

CONCLUSIONS

Although generally thought to cause mild disease, common coronaviruses are also associated with significant morbidity in adults. Our data show that even before the COVID-19 pandemic, common coronaviruses were associated with worse outcomes compared to influenza. These findings may help identify a subset of patients who are more susceptible to poor outcomes from common coronavirus infections. A better understanding of outcomes related to common coronaviruses versus influenza may clarify the biology and help plan for clinical interventions for patients with suspected infection. Apart from SARS-CoV-2, routine viral testing for patients who come into contact with the health care system could not only provide more accurate epidemiologic data but also help with prognosis and potential treatment for patients with worsening respiratory symptoms.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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Potential conflicts of interest. D. M. W. performed clinical trials with BioFire and Cepheid within the past 3 years. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure

of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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