ORIGINAL ARTICLE

Prevalence and Predictors for Respiratory Viral Infections among Liver Disease Patients

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Abstract

Aim and background: Respiratory viral infections (RVIs) cause significant hospitalizations every year. Also, RVIs caused by either influenza or noninfluenza group of viruses can have adverse outcomes, especially among immunosuppressed patients. Regular and timely supervision is needed for accurate etiological identification, to prevent inappropriate use of antibiotics in patients with nonbacterial etiology. This study aimed to identify the spectrum of RVIs and clinical characteristics among liver disease patients with influenza-like illness (ILI).

Materials and methods: In this study, medical records of patients with ILI, whose requests for respiratory viral testing came from September 2016 to December 2022 were retrospectively reviewed. Respiratory viruses were identified using FilmArray 2.0 respiratory panel (BioFire Diagnostics, USA).

Results: Of the 1,577 liver disease patients with ILI, the overall prevalence of RVI was 28% ($n = 449$). Infection by noninfluenza viruses (NIVs) was detected in 329 patients (73%), higher than those infected with influenza viruses. In multivariable logistic regression analysis, female gender [odds ratio (OR): 2.5, 95% confidence interval (CI): 1.5–4.2], infection with influenza B (OR: 3.3, 95% CI: 1.09–9.9) and decompensated cirrhosis (OR: 3.9, 95% CI: 1.7–8.5) were independent risk factors for mortality. Regarding seasonality, influenza peaked in monsoons and winters, whereas NIVs circulated throughout the year.

Conclusion: Overall, this study adds new knowledge regarding the incidence of RVI and the distribution of respiratory viral etiologies among liver disease patients with ILI. The findings highlight that female gender, decompensated cirrhosis, and influenza B infection are independently associated with poor clinical outcomes. Early etiological identification of viral causes of ILI could aid in an enhanced understanding of the prevalence of ILI and the timely management of the patients.

Clinical significance: Respiratory viral infections can cause severe illness in individuals with underlying liver disease. Accurate diagnosis and risk stratification is crucial in mitigating the adverse health effects.

Keywords: Cirrhosis, Gender, Influenza, Liver, Noninfluenza, Respiratory viral infection, Seasonality.

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Introduction

Acute respiratory tract infection (ARTI) is a proven infectious cause of mortality among children (<5 years) and varies geographically and seasonally significantly across the globe. Viruses are the most common cause of ARTI, leading to infections termed "respiratory viral infections" (RVI). Respiratory viral infection is observed to be around 10–23% of total hospital-acquired pneumonia (HAP) among adults.[1] The role of RVI in modulating disease severity and the clinical outcome depends on several factors, including the type of viral infection, age, and underlying comorbidity.[2] Although influenza virus infection (IVI) predominates among RVI, other noninfluenza virus infections (NIVI) are increasingly identified as primary etiological agents for respiratory diseases. The most common viruses in the NIV category include respiratory syncytial virus (RSV), parainfluenza virus, human coronaviruses, human metapneumovirus (MPV), and adenovirus.[1] Rhinoviruses are often the most common viruses found in upper respiratory tract infections.[3] Coronaviruses have been known to cause severe ARTI, and the unprecedented SARS-CoV-2 pandemic underscores the importance of identifying existing and emerging NIVI-causing respiratory diseases.[4–6] Early and accurate diagnosis of RVI can lead to the prevention of inappropriate use of antibiotics.

Timely and properly isolating infected patients is essential, especially in intensive care facilities to prevent further spread of infection.[7,8] An underlying comorbid condition, including advanced chronic liver disease could influence the incidence of pneumonia and its impact on the overall clinical outcome.[9] In line with previous reports, IVI in patients with pre-existing liver disease

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might be associated with severe clinical outcomes.[10,11] Although the prevalence of NIVI is expected in the adult population, only limited attention is paid to the clinical outcomes associated with NIVI.[12] Moreover, the burden of NIVI among hospitalized patients is not assessed. Lack of access to testing, vaccination, and specific antiviral medications, further decrease the importance of diagnosing virus-induced pneumonia among adults. Moreover, data describing the prevalence of RVI in patients with underlying liver diseases is still limited. Therefore, in this retrospective study, we attempted to evaluate the incidence of RVI in liver disease patients and better understand the risk factors associated with mortality among these patients.

Materials and Methods

Study Population

The medical records of patients with underlying liver disease and influenza-like illness (ILI), who visited the hospital between September 2016 and December 2022, were retrospectively reviewed and included. The data regarding the study population's demographic, biochemical, and clinical details were reviewed from the hospital information system (HIS). Patients with SARS-CoV-2 positive status and with incomplete clinical information were excluded from our study. The following clinical definitions were used in our study:

- The ILI: An acute respiratory illness with a measured temperature of ≥38°C and cough, with onset within the past 10 days.[13]
- Cirrhosis: A diffuse process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules.[14]
- Decompensated cirrhosis: Decompensation in cirrhosis is marked by overt clinical signs, including ascites, bleeding, encephalopathy, and jaundice.[15]

Respiratory Viral Testing

The combined throat and nasal swabs in viral transport media (VTM) for respiratory virus testing were collected as per our routine laboratory practice.[16] A panel of 18 respiratory viruses by real-time polymerase chain reaction (RT-PCR) on FilmArray 2.0 instrument (BioFire Diagnostics, Utah, USA) was evaluated as per the manufacturer's instructions.[17] The panel included adenovirus, coronavirus 229E (CoV-229E), coronavirus HKU1 (CoV-HKU1), coronavirus OC43 (CoV-OC43), coronavirus NL63 (CoV-NL63), MPV, human rhinovirus/enterovirus, influenza A (flu A), influenza A/H1 (flu A/H1), influenza A/H1-2009 (flu A/H1-2009), influenza A/H3 (flu A/H3), influenza B (flu B), Middle East respiratory syndrome coronavirus (MERS-CoV), parainfluenza 1 (PIV1), parainfluenza 2 (PIV2), parainfluenza 3 (PIV 3), parainfluenza 4 (PIV 4), and RSV.

Statistical Analysis

Qualitative variables were presented in frequencies and proportions, whereas quantitative variables were described in median with interquartile range (IQR). Asymmetry, kurtosis, and Kolmogorov–Smirnov test values were studied to determine the data distribution. Comparison between different groups was done using the Chi-square test. Also, $p < 0.05$ was considered the cut-off for statistical significance. Binary logistic regression was applied to determine the independent statistically significant relationship between determinant variables and study groups. Multivariable logistic regression was carried out to calculate adjusted odds ratios (ORs) for factors that demonstrated an association with $p < 0.2$ on bivariable analysis.

Results

Baseline Characteristics of the Study Population

The study included 1,577 patients with an underlying liver disease and symptomatic ILI. Most of the population were adults (n = 1567/1577, 99%). A male predominance of 79% (n = 1239/1,577) and a median age of 48.7 years (IQR: 38–59 years) was seen. Patients with liver cirrhosis were observed to be higher (n = 1212/1577, 77%). An overall prevalence of RVI was 28% (n = 449/1577; Flowchart 1), with the majority being adults (adults n = 441/449, 98% vs children n = 8/449, 2%).

Characteristics of Patients with Respiratory Viral Infection

Among the patients positive for RVI, 27% (n = 120/449) were positive for IVI, whereas 73% (n = 329/449) were positive for NIVI (Flowchart 1). In the IVI group, the incidence of influenza A was higher (n = 101/120, 84%) than influenza B (n = 19/120, 16%). In the NIVI group, human enterovirus/rhinovirus was the most common (n = 179/329, 54%), followed by RSV (n = 45/329, 14%). The clinical symptoms such as cough (49.2%), fever (52.5%), and difficulty in breathing (49.2%) were significantly higher in the IVI group than that of NIVI group ($p < 0.05$; Table 1). No statistically significant difference was seen between the groups concerning age, admission type, underlying etiology for liver disease, AST levels, length of hospital stay, a requirement of oxygen supply, and mortality (Table 2).

Risk Factors Associated with the Occurrence of Respiratory Viral Infection

Among the RVI-positives (n = 449), on univariate regression analysis, liver cirrhosis (OR: 1.35, 95% CI: 1.03–1.77) and female gender (OR: 2.7, 95% CI: 2.2–2.08) were associated with the occurrence of RVI (Supplementary Table 1). On multivariable regression analysis, liver cirrhosis (OR: 1.39, 95% CI: 1.05–1.83, $p = 0.01$) and female gender (OR: 2.8, 95% CI: 2.2–3.6, $p < 0.001$) were independently associated with the occurrence of RVI (Supplementary Table 1).

Predictors of Mortality in Respiratory Viral Infection

To determine risk factors for mortality in liver disease patients with RVI (n = 449), univariate regression analyses revealed the following factors to be associated with mortality: Female gender (OR: 2.4, 95% CI: 1.6–3.8, $p < 0.001$), infection with influenza A (OR: 3.3, 95% CI: 1.09–9.9, $p < 0.05$), infection with influenza B (OR: 0.53, 95% CI: 0.31–0.94, $p < 0.05$), decompensated cirrhosis (OR: 3.9, 95% CI: 0.23–0.66, $p < 0.001$) and acute-on-chronic liver failure/acute liver failure (ACLF/ALF) as an underlying liver disease etiology [OR: 2.068, 95% CI: 1.05–4.06, $p < 0.03$] (Table 3).

On multivariable regression analysis, female gender (OR: 2.5, 95% CI: 1.5–4.2, $p < 0.001$), infection with influenza B (OR: 3.3, 95% CI: 1.09–9.9, $p < 0.05$), decompensated cirrhosis (OR: 3.9, 95% CI: 0.23–0.66, $p < 0.001$) and ACLF/ALF (OR: 2.068, 95% CI: 1.05–4.06, $p < 0.03$) (Table 4) were independent risk factors for mortality.

Seasonal Distribution of Respiratory Viral Infection Cases

In an attempt to understand the seasonal patterns of RVI, the monthly and yearly distribution of IVI and NIVI cases in our study period was evaluated (Fig. 1). The peak of IVI cases was seen

Flowchart 1: A flowchart of study design

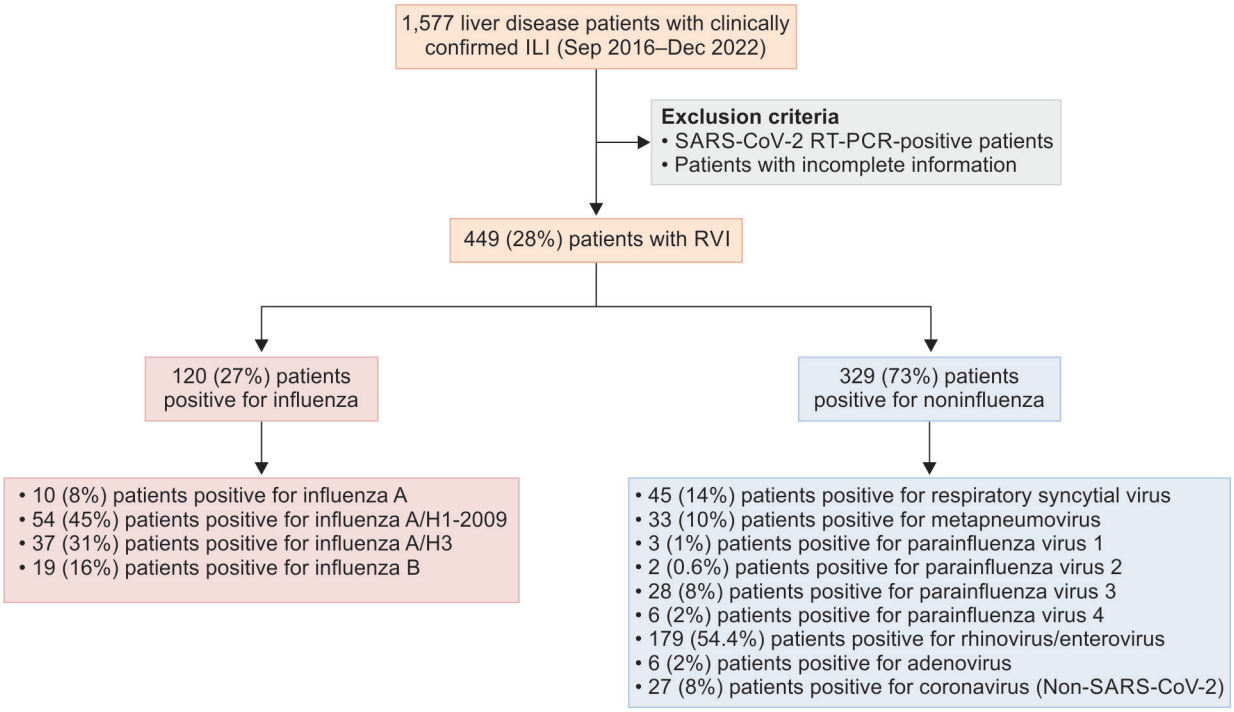

Table 1: The overall characteristics of the study population ($n = 1,577$)

Characteristics $n = 1577$	*RVI* $n = 449$	*Non-RVI* $n = 1128$	*p-value*
Gender			
Male	295 (65.7)	944 (76.2)	<0.001
Age (years, median)	48.5 (IQR: 38–60)	49 (IQR: 39–59)	0.747
Inpatient	443 (98.7)	1112 (98.6)	0.900
Cirrhosis	361 (80.6)	851 (75.4)	0.029
Outcome–mortality	118 (26.3)	339 (30.1)	0.136

RVI, respiratory viral infection, Values given in brackets are in percentages/IQR

postmonsoon (August–September) and during the winter season (December–February), which is congruent with findings from previous studies.[18,19] However, cases positive for NIVI occurred throughout the year, with a surge in infections observed during the winters. With the advent of the COVID-19 pandemic from March 2020 onward, a dip was seen in overall positivity in both IVI and NIVI at our center, coinciding with previous findings. Subsequently, from June 2021 onward, a sharp increase in NIVI cases was observed compared to previous years. Increased public awareness, lowered COVID-19-positive cases, and escalated use of differential diagnosis methods might be implied for increased detection of NIVI.

Discussion

The present study investigated the incidence of RVI among liver disease patients with ILI symptoms. IVI and NIVI were compared, and risk factors for mortality were assessed. Moreover, in a unique attempt, the seasonality of the occurrence of IVI and NIVI was also investigated.

This study reported a RVI incidence of 28% in the study population. There is limited literature describing the incidence of RVI in liver disease patients. Earlier, a previous study from our center had reported 22.2% of RVI among patients with underlying liver cirrhosis.[20]

Among the study population, the incidence of NIVI (73%) was higher as compared to IVI (27%). Rhinovirus/enterovirus was the most dominant (54%) among the NIVI group, and influenza A/HINI virus was the most prevalent infection (64%) in the IVI group. No significant difference was seen between IVI and NIVI in context to gender, age, underlying liver status, underlying liver etiology, and length of hospitalization. The overall in-hospital mortality observed among RVI patients was 26%. Further, to understand the association of any risk factor with poor clinical outcome, we found that female gender (OR: 2.5, 95% CI: 1.51–4.2), decompensated cirrhosis (OR: 3.91, 95% CI: 1.79– 8.5, $p < 0.05$) and Infection with Influenza B (OR: 3.3, 95% CI: 1.09–9.9, $p < 0.05$) were independent risk factors associated with more than 2-fold increase in mortality among liver disease patients with RVI.

Several studies have correlated gender differences to clinical outcomes in influenza-positive patients.[21,22] A study by Klein et al. has shown differences in immune responses to influenza vaccination between males and females.[23] The role of sex hormones in regulating immune responses, in part, might contribute to the observed findings. These findings indicate the implementation of mechanistic studies to understand better the differences in immune responses between different genders to RVI, which could shed more light on the impact of gender on poor clinical outcomes. A growing body of literature has demonstrated that decompensated cirrhosis is an independent risk factor of mortality,[9,24] owing to underlying multifactorial immune dysfunction. Recently, a study by Liu et al. identified influenza B and liver cirrhosis as independent risk factors of mortality, further corroborating this study's findings.[25]

Table 2: The baseline and clinical characteristics of patients in IVI and NIVI group

Characteristics (RVI group)	*IVI (n = 120)*	*Non-IVI (n = 329)*	*p-value*
Gender *n* (%)			
Male	74 (61.7)	221 (67.2)	0.277
Age [years, median (IQR)]	54 (39.25–61.75)	48 (38–59)	0.116
Underlying liver etiology *n* (%)			
CLD-HBV/HCV/Ethanol	48 (40.0)	163 (49.5)	0.073
ACLF/ALF	16 (13.3)	50 (15.2)	0.622
CLD-NASH	30 (25.0)	62 (18.8)	0.153
CLD-others	21 (17.5)	47 (14.3)	0.400
Others	5 (4.2)	7 (2.1)	0.318
Underlying liver status *n* (%)			
Compensated cirrhosis	10 (8.3)	9 (2.7)	0.009
Decompensated cirrhosis	85 (70.8)	259 (78.7)	0.080
No cirrhosis	25 (20.8)	61 (18.5)	0.585
Symptoms *n* (%)			
Cough	59 (49.2)	117 (35.6)	0.009
Cold	47 (39.2)	107 (32.5)	0.189
Fever	63 (52.5)	125 (38.0)	0.006
Breathing difficulty	59 (49.2)	125 (38.0)	0.033
AST [IU/mL, median (IQR)]	81 (50–124.5)	75 (45–154)	0.093
ALT (IU/mL, median [IQR])	37.5 (26–60.5)	38.5 (23–65.75)	0.042
Length of hospitalization (days, median[IQR])	8.5 (5–16.75)	10 (5.5–18)	0.099
Requirement of oxygen, *n* (%)	64 (53.3)	143 (43.5)	0.063
In-hospital mortality, *n* (%)	29 (24.2)	89 (27.1)	0.539

ALF, acute liver failure; ACLF, acute-on-chronic liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; IVI, influenza viral infection; NASH, non-alcoholic steatohepatitis, Non-IVI, noninfluenza viral infection

Table 3: Determinants of mortality in RVI group–crude OR (univariate regression analysis)

Factor	*Unadjusted OR*	*95% CI*	*p-value*
IVI	0.859	0.530–1.394	0.539
Gender (male)	0.403	0.261–0.620	<0.001
Age	0.991	0.977–1.005	0.194
Viral etiology			
Flu A, A/H1-2009, A/H3	0.538	0.307–0.942	0.028
Flu B	4.151	1.627–10.590	0.003
RSV	1.461	0.756–2.824	0.257
MPV	1.056	0.476–2.343	0.893
PIV1, PIV2, PIV3, and PIV4	0.828	0.381–1.801	0.634
Rhinovirus/enterovirus	0.951	0.619–1.463	0.819
Adenovirus	1.409	0.255–7.797	0.656
Coronavirus	1.194	0.508–2.806	0.683
Underlying liver etiology			
CLD-HBV/HCV/ethanol	1.291	0.848–1.967	0.233
ACLF/ALF	1.757	1.011–3.054	0.044
CLD-NASH	0.625	0.355–1.099	0.101
CLD-others	0.764	0.412–1.415	0.391
Others	0.730	0.690–0.773	0.042
Underlying liver status			
Compensated cirrhosis	0.725	0.148–3.547	0.692
Decompensated cirrhosis	2.672	1.392–5.128	0.003
AST (IU/mL)	1.000	1.000–1.000	0.951
ALT (IU/mL)	1.000	0.999–1.001	0.905
Requirement of oxygen	0.854	0.559–1.304	0.465

ACLF, acute-on-chronic liver failure; ALF, acute liver failure; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CLD, chronic liver disease; Coronavirus included, Coronavirus 229E (CoV229E), Coronavirus HKU1 (CoVHKU1), Coronavirus NL63 (CoVNL63), Coronavirus OC43 (CoVOC43); Flu A, influenza A; Flu A/H1-2009, influenza A/H1-2009; Flu A/H3, influenza A/H3; Flu B, influenza B; IVI, influenza viral infection; HBV, hepatitis B virus; HCV, hepatitis C virus; MPV, human metapneumovirus; NASH, non-alcoholic steatohepatitis; PIV1, parainfluenza 1; PIV2, parainfluenza 2; PIV3, parainfluenza 3; PIV4, parainfluenza 4; RSV, respiratory syncytial virus

Moreover, a previous study from our center had established a positive association between the occurrence of Influenza A and severe clinical outcomes in chronic liver disease patients.[26] Therefore, timely identification of the etiology of RVI in liver disease patients and subsequent proper clinical management is crucial to reduce severity. Earlier studies have highlighted the role of multiplex RT-PCR based assays as quick and accurate diagnostic

Table 4: Determinants of mortality in RVI group–Adjusted OR (multivariable regression analysis)

Factor	*Adjusted OR*	*95% CI*	*p-value*
Gender	0.396	0.237–0.661	<0.001
(male)			
Age	0.996	0.978–1.014	0.682
Viral etiology			
Flu A, A/H1-2009, A/H3	0.729	0.39–1.350	0.315
Flu B	3.300	1.094–9.961	0.034
Underlying liver etiology			
ACLF/ALF	2.068	1.053–4.060	0.035
CLD-NASH	0.643	0.337–1.226	0.180
Underlying liver status			
Compensated cirrhosis	2.071	0.369–11.622	0.408
Decompensated cirrhosis	3.916	1.795–8.543	0.001

ACLF, acute-on chronic liver failure; ALF, acute liver failure; CLD, chronic liver disease; Influenza A/H1-2009; Flu A/H3, influenza A/H3; Flu B: Influenza B; IVI, influenza viral infection; NASH, non-alcoholic steatohepatitis

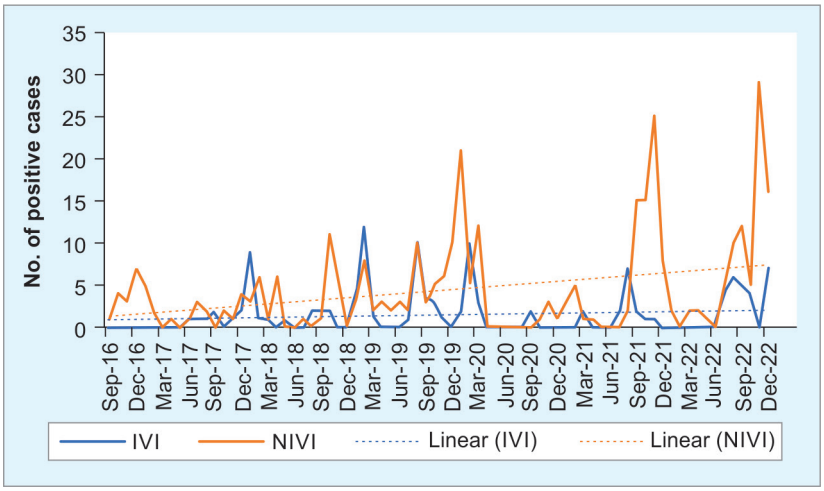

Fig. 1: A line graph showing incidence and seasonal variations of IVI and NIVI in our study population

assays compared to the routine culture and antigen detection methods for rapid diagnosis of RVI.[27–34] Although multiplex panels are faster, their high cost and maintenance restricts their use in developing countries with resource-limited settings.

In addition to risk factors, overall, a seasonal pattern of IVI and NIVI was also evaluated. The findings in the present study showed that the IVI peaked during the monsoon followed by the winter season, in accordance with previously reported studies.[18,19] However, the usual circulation of IVI remained low during the COVID-19 pandemic period (April 2020–June 2021), which aligned with India's surveillance data (https://ncdc.gov.in/) and worldwide epidemiological data.[35] Social distancing, wearing masks, rechanneling clinical testing and viral interference (a phenomenon where one virus inhibits the survival and replication of another coinfecting virus) might have resulted in low reported cases in 2020–2021. Also, IVI is a known risk factor for developing severe acute respiratory illness among the elderly and immunocompromised individuals.[26,36,37] Therefore, the influenza vaccination strategy should be strictly adhered to, most importantly, for patients with underlying comorbidities, including liver disease, heart disease and diabetes. The best optimal time for annual influenza vaccination should be April–May, at least 2 months before the peak, to offer optimum protection to patients with comorbidities.

Now, regarding NIVI, no particular seasonality was observed as its circulation was seen throughout the year. Nevertheless, the peak of NIVI was observed during winter. Infection with NIVI, especially in patients with underlying immune modifying illness, depends mainly on an individual's immune status rather than the pathogen's community prevalence. Local pollution, topography, and meteorological factors can further contribute to an increase in NIVI. There is still a paucity of literature on the clinical presentation of NIVI, especially among comorbid patients. Large-scale clinical and epidemiological studies are warranted to address the socioeconomic burden associated with NIVI.

In general, IVI and NIVI attack the respiratory tract and alter its commensal microbiota, predisposing the host to secondary infections.[38] Secondary bacterial/fungal infections often severely impact patients with cirrhosis.[39] As patients with liver cirrhosis have impaired immune system, it is vital to identify RVI for timely and

appropriate management to avoid a prolonged hospital stay due to secondary infections.

The limitation of this study is that it is a single-center retrospective laboratory-based study where those liver disease cases with ILI were included, in which a request for respiratory viral testing was generated. Despite this, this study adds significantly to the current literature by evaluating the incidence of RVI among liver disease patients and the association of risk factors with poor clinical outcomes.

Conclusion

Taken together, this study highlights the increased risk of mortality of females with underlying liver disease and RVI. Influenza B, being associated with higher mortality, should be investigated further. Moreover, it is essential to understand the impact of gender differences and underlying health conditions in viral infections, especially while designing vaccination and treatment strategies. Epidemiological and clinical surveillance of RVI should be implemented and examined in greater detail to understand their pathogenesis and pathophysiology. Information on changes in seasonality and community circulation of RVI is vital for timely, appropriate healthcare interventions. Prompt testing and referral for immunocompromised patients with ILI should be implemented.

Clinical Significance

Female gender, infection with influenza B, and decompensated cirrhosis are associated with poorer clinical outcomes among liver disease patients with RVI. Early diagnosis, epidemiological tracing and appropriate therapeutic measures for RVI are required to improve patient care and management, especially among comorbid patients.

Ethical Approval

The Institutional Review Board (Institutional Ethics Committee, Institute of Liver and Biliary Sciences, New Delhi, India) reviewed and approved the study (Ethical Approval Number: IEC/2021/84/MA10). It was conducted as per the principles of the Declaration of Helsinki. The Institutional Review Board waived patient informed consent because the study was based on retrospective clinical data analysis. Patient records or information were anonymized and de-identified before analysis.

Supplementary Material

The supplementary table is available online on the website of https://www.ejohg.com/journalDetails/EJOHG.

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