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REVIEW

Individuals at risk for severe COVID-19 in whom ritonavir-containing therapies are contraindicated or may lead to interactions with concomitant medications: a retrospective analysis of German health insurance claims data

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Abstract

Background: Nirmatrelvir/ritonavir is authorized for the treatment of COVID-19 but has several contraindications and potential drug–drug interactions (pDDIs) due to ritonavir-induced irreversible inhibition of cytochrome P450 3A4. We aimed to assess the prevalence of individuals with one or more risk factors for severe COVID-19 along with contraindications and pDDIs due to ritonavir-containing COVID-19 therapy.

Methods: Retrospective observational study of individuals with one or more risk factors according to Robert Koch Institute criteria for severe COVID-19 according to German statutory health insurance (SHI) claims data from the pre-pandemic years 2018–2019 based on the German Analysis Database for Evaluation and Health Services Research. Prevalence was extrapolated to the entire SHI population using age-adjusted and sex-adjusted multiplication factors.

Results: Nearly 2.5 million fully insured adults, representing 61 million people in the German SHI population, were included in the analysis. In 2019, prevalence of individuals that would have been at risk of severe COVID-19 was 56.4%. Amongst them, the prevalence of contraindications for treatment with ritonavir-containing COVID-19 therapy was approximately 2% according to presence of somatic comorbidities (severe liver or kidney disease). Prevalence of intake of medicines contraindicated for their potential interactions with ritonavir-containing COVID-19 therapy was 16.5% according to Summary of Product Characteristics and 31.8% according to previously published data. The prevalence of individuals at risk of pDDIs during ritonavir-containing COVID-19 therapy without adjustment of their concomitant therapy was 56.0% and 44.3%, respectively. Prevalence data for 2018 were similar.

Conclusion: Administering ritonavir-containing COVID-19 therapy can be challenging as thorough medical record review and close monitoring are required. In some cases, ritonavir-containing treatment may not be appropriate due to contraindications, risk of pDDIs, or both. For those individuals, an alternative ritonavir-free treatment should be considered.

Keywords: comorbidity, contraindication, COVID-19, drug–drug interactions, health insurance claims, ritonavir.

Citation

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Introduction

COVID-19, caused by SARS-CoV-2, has spread globally and was declared a global pandemic on 11 March 2020 by the World Health Organization.[1] As the first case in Germany was identified on 27 January 2020,[2,3] the disease spread rapidly throughout the country with a total of more than 36 million cases and over 159,000 deaths recorded up to mid-December 2022.[4] People who are older, male, with obesity, immunocompromised, and

have one or more comorbidities, including hypertension, diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, chronic kidney disease (CKD) and malignancy, have an increased risk for severe COVID-19 and a negative health outcome.[5–10] Furthermore, people with comorbidities commonly take several drugs, which might lead to drug–drug interactions (DDI) with COVID-19 pharmacotherapy. Therefore, patients with COVID-19 and comorbidities should be managed carefully to avoid potential DDIs (pDDIs).

Combination nirmatrelvir/ritonavir was authorized for use in the treatment of COVID-19 in the European Union (EU) by the EMA in January 2022.[11] In the USA, the FDA issued an Emergency Use Authorization for nirmatrelvir/ritonavir for the treatment of mild-to-moderate COVID-19 in adults and paediatric patients (12 years of age and older, weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.[12] The antiviral drug ritonavir is a protease inhibitor that irreversibly inhibits cytochrome P450 (CYP) 3A4 (CYP3A4), an enzyme important for the metabolism of drugs,[13] which is a significant cause of DDIs.[14] As nirmatrelvir is primarily metabolized by CYP3A4,[15] combination nirmatrelvir/ritonavir is subject to DDIs with other inducers and inhibitors of the enzyme,[16] and caution is required for use of nirmatrelvir/ritonavir in the management of COVID-19.[17] Adverse pharmacokinetic DDIs may occur when drugs that are substrates, inducers and/or inhibitors of the same metabolizing enzymes are coadministered, potentially altering the expected rate of metabolism of one or both compounds. The clinical consequences can range from a lack of therapeutic efficacy to severe toxicity and, in extreme cases, fatality.[18]

As many drugs, such as lipid-lowering agents, antiarrhythmics, cardiovascular drugs, anticonvulsants and anticoagulants, are metabolized by CYP3A4, pDDIs have high clinical importance.[19] They can lead to harmful effects, such as QTc prolongation,[20,21] with the risk of cardiac events, including cardiac arrhythmias such as Torsade-de-Pointes tachycardia.[22,23]

Several studies identified DDIs and pDDIs in patients with COVID-19 receiving pharmacotherapy. An observational Spanish study reported that 87.4% of hospitalized patients (152/174) with COVID-19 experienced DDIs, including 417 DDIs detected between COVID-19-related drugs and concomitant hospital medication. Lopinavir/ritonavir, an investigational regimen for COVID-19, accounted for 43.2% of these detected DDIs. Comorbidities and polypharmacy were independent risk factors associated with DDI development.[23] Similarly, another Spanish cross-sectional study found that the prevalence of pDDIs in hospitalized patients with COVID-19 undergoing treatment with lopinavir/ritonavir was 62.3% (225/361). Risk factors associated with presenting one or more potential interactions in patients receiving lopinavir/ritonavir included older age (>65 years), intensive care unit admission, previous respiratory and psychiatric disorders, dyslipidaemia, and the number of prescribed drugs.[24] A third Spanish cross-sectional study of patients positive for SARS-CoV-2 attending a single centre reported that 97/125 (78%) patients prescribed lopinavir/ritonavir had pDDIs with concomitant medications, including 26% with major DDIs.[19] A retrospective Italian study of hospitalized patients with COVID-19 found that lopinavir/ritonavir was one of the main drivers of potentially severe DDIs during hospitalization, mainly due to an increased risk of cardiotoxicity.[23]

As the number of COVID-19 cases is still high and new treatments emerge, data to inform and optimize COVID-19 management are needed, especially for individuals at high risk of severe disease outcomes following infection with SARS-CoV-2 and/or side-effects of specific drug therapy.

Combination nirmatrelvir/ritonavir is currently the only oral COVID-19 therapy authorized in the EU. It is indicated for adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19. However, the combination contains ritonavir and, therefore, has several contraindications and pDDIs according to the Summary of Product Characteristics (SmPC), which represents the regulatory assessment by EMA.[25] The likelihood of clinically significant DDIs between therapeutic agents against COVID-19 and commonly prescribed comedications can be monitored and predicted by the University of Liverpool's COVID-19 Drug Interactions online resource.[26] Moreover, a German group of clinical pharmacologists and pharmacists provided a detailed assessment of medications that may cause pDDIs with ritonavir-containing COVID-19 treatments and which are commonly prescribed in Germany.[27] The paper by Mikus et al.[27] contains a clear tabular substance list with recommendations for action for planned therapy with nirmatrelvir/ritonavir and is available online as an open-access publication.

The aim of this retrospective study was to assess the prevalence of one or more risk factors for progression to severe COVID-19 amongst individuals with contraindications (due to pre-existing comorbidities and/or comedications) and pDDIs due to ritonavir-containing COVID-19 therapy.

Methods

Data source

The study retrospectively analysed German statutory health insurance (SHI) claims data from 2018 to 2019 (i.e. prior to the COVID-19 pandemic) in the German Analysis Database for Evaluation and Health Services Research (DADB), administered by Gesundheitsforen Leipzig GmbH. Approximately 70 million people in Germany are insured in the SHI system, representing about 90% of the German population. The DADB consists of approximately 3.5 million individuals (5% of the SHI population) and covers the period from 2013 to 2021. Health claims data are provided by 16 statutory healthcare insurers and include patient characteristics, diagnoses for hospitalized patients and outpatients (International Classification of Diseases 10th revision codes, German Modification (ICD-10-GM)),[28] drug prescriptions (ATC Level 5 codes), and cost information. For most individuals, information such as procedures and diagnosis-related groups (DRG) is also available. Data in the DADB are similar to those of the total population in the German SHI system and have been shown to be a representative sample of the general German population.[29] This is ensured by annual comparison against data published by the German Federal Social Insurance Office (Bundesamt für Soziale Sicherung (BAS)). The DADB has been used successfully in submissions to the German Health Technology Assessment (HTA) authorities to describe patient demographics in several indications as part of the benefit–risk assessment of medicinal products.[30–33]

Inclusion and exclusion criteria

This study included adult individuals covered under SHI and had one or more risk factors for severe COVID-19 according to Robert Koch Institute (RKI) criteria[34] in the DADB for the calendar years of 2018 and 2019. Adults aged ≥60 years and those aged ≥18 years and with at least two outpatient diagnoses in two quarters per calendar year (M2Q criterion) or one inpatient diagnosis were included in the study. Risk factors for severe COVID-19 were identified by ICD-10-GM diagnostic codes[28] for obesity, cardiovascular diseases (including hypertension, heart failure, coronary artery disease, cardiomyopathies, atrial fibrillation and flutter, and cerebrovascular disease), chronic lung disease (including chronic obstructive pulmonary disease, interstitial lung disease and other severe chronic lung diseases), chronic liver diseases (including cirrhosis, hepatic insufficiency and autoimmune hepatitis), CKD (including chronic renal failure, dialysis and renal failure), Down's syndrome, neurological and psychiatric diseases (including dementia, epilepsy, neurological diseases, severe mental health disorders, Parkinson's disease, depression, and intellectual and developmental disabilities), diabetes mellitus type 1 and type 2, cancer (including metastatic solid tumours, haemato-oncological diseases, and solid tumours (excluding melanoma)), and patients with a compromised immune system (based on Zimmermann et al.[35]; including post-organ transplantation, congenital immunodeficiency, ulcerative colitis, Crohn's disease, HIV, and rheumatoid arthritis). ICD-10-GM diagnostic codes are shown in Supplementary Material 1 (available at: https://www.drugsincontext.com/wp-content/uploads/2023/06/dic.2023-3-4-Suppl.pdf). Insured persons were selected per calendar year and were required to have full health insurance coverage in the reporting year (2018 or 2019). Of note, HIV is a potential risk factor for severe COVID-19;[34] therefore, patients receiving ritonavir as part of their antiretroviral therapy were included in the study. Pregnant and breastfeeding women were excluded from the study.

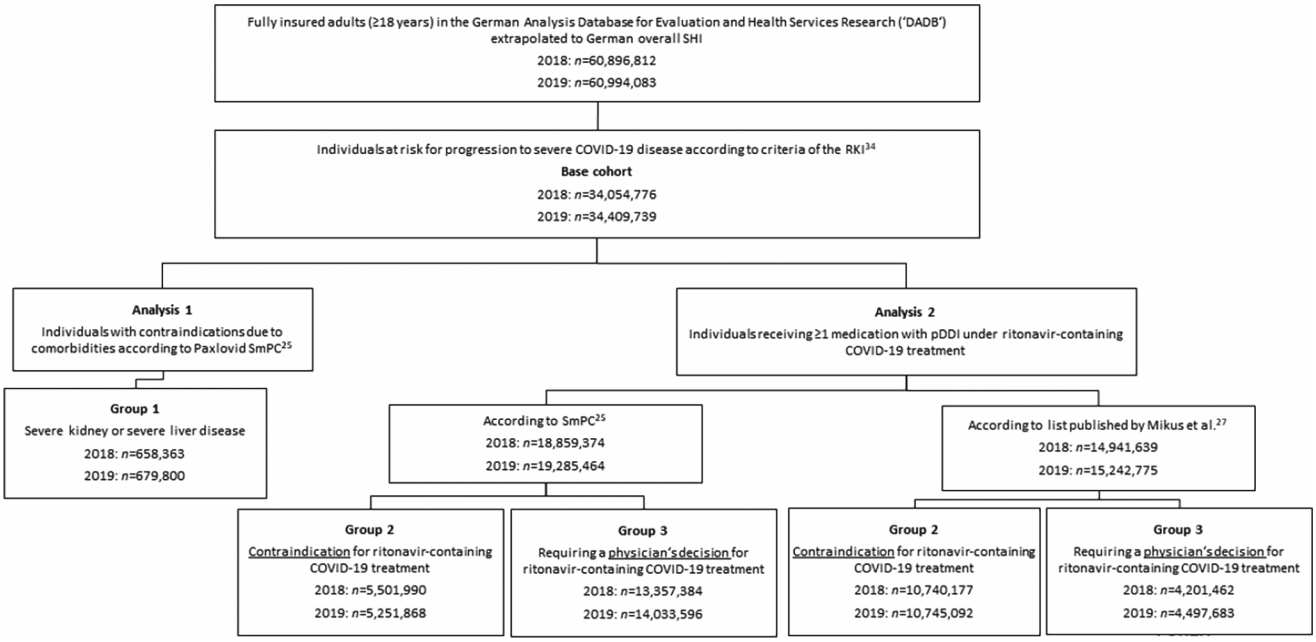
Statistics

As the DADB represents an approximate 5% sample of the total population of SHI in Germany, the results were extrapolated using extrapolation factors. For this purpose, the age and sex distribution in the DADB was compared with BAS data to determine age-adjusted and sex-adjusted multiplication factors.[36] The age and sex distribution of individuals in the DADB and the SHI population in the years of study (2018 and 2019) were comparable (Supplementary Material 2).

Using the extrapolated base cohort, two separate analyses were performed using German SHI claims data (Figure 1). The first analysis included individuals with a comorbidity for which ritonavir-containing treatment for COVID-19 is contraindicated according to the nirmatrelvir/ritonavir SmPC.[25] Individuals with severe liver or kidney disease were identified using ICD-10-GM codes:[28] acute and sub-acute hepatic failure (K72.0); liver cirrhosis, stage Child-Pugh C (K74.72); CKD, stage 4 (N18.4); CKD, stage 5 (N18.5); or chronic renal failure, unspecified (N18.9). The second analysis included individuals receiving at least one medication that may interact with ritonavir (Supplementary Material 3). The comedications were selected based on ATC codes (with the exception of midazolam, which was analysed by pharmaceutical registration number (Pharmazentralnummer; PZN) to differentiate between oral and parenteral routes) and excluding medicinal products for dermal, ophthalmological, and otological use. ATC codes were used to include the active substance and possible combinations.

Based on either the nirmatrelvir/ritonavir SmPC[25] or the list of medications with a potential interaction with nirmatrelvir/ritonavir that was published by Mikus et al.,[27] where drugs were classified into six categories of

Figure 1. Disposition of individuals at risk for severe COVID-19 in the German Analysis Database for Evaluation and Health Services Research (DADB) extrapolated to the entire German statutory health insurance (SHI) population.



recommendations for action ranging from Category 1 (no dose adjustment; monitoring, where appropriate) to Category 6 (if possible, omit ritonavir), individuals were assigned to three groups (Figure 1): (1) patients with contraindications due to somatic comorbidities (Analysis 1), (2) patients with contraindications due to comedications, and (3) patients who would require a physician's decision about adjusting or temporarily discontinuing a concomitant therapy. By this approach, it is possible that individuals who were assigned to Group 1 (somatic comorbidities) may also have been assigned to Group 2 (contraindicated comedications) or Group 3 (comedications requiring physician's decision), for example, individuals who had impaired renal function and were also taking medications that had pDDIs with nirmatrelvir/ritonavir. Individuals with polypharmacy who were assigned to Group 2 (contraindicated comedications) were not additionally counted in Group 3 (comedications requiring physician's decision). The nirmatrelvir/ritonavir SmPC list contains 182 ATC codes consisting of 39 (including 35 active pharmaceutical ingredients (APIs)) in the 'contraindication' category and 143 (75 APIs) in the 'physician's decision' category. The list published by Mikus et al.[27] contains 165 ATC codes comprising 102 (83 APIs) in the 'contraindication' category and 63 (31 APIs) in the 'physician's decision' category. Finally, a unified analysis was performed to estimate the number of individuals with a contraindicated pre-existing medical condition and/or risk of pDDIs for whom administration of nirmatrelvir/ritonavir would be inappropriate.

All analyses were performed using Microsoft SQL Server Management Studio version 14.0.17254.0 and Microsoft Excel 2019.

Ethics and informed consent

As the study used retrospective anonymized, aggregated SHI claims data, which posed no risk to individuals included in the analysis nor risk of personal data disclosure, no independent Ethics Committee submissions or approval or patient consent were required for the study.

Results

The DADB included nearly 2.5 million fully insured adults for each of the calendar years 2018 (n=2,444,492) and 2019 (n=2,470,018). Extrapolated to the overall German SHI population, this represents nearly 61 million insured adults (60,896,812 and 60,994,083, respectively).

After inclusion and exclusion criteria were applied, approximately 1.3 million fully insured adult individuals in the DADB were identified as having at least one risk factor for severe COVID-19: 1,281,055 (52.41%) in the 2018 base cohort and 1,315,806 (53.27%) in the 2019 cohort. This represents over 34 million of the overall German SHI population with a prevalence of approximately 56%: 34,054,776 (55.92% of the SHI population) and 34,409,739 (56.41%), respectively (Figure 1). For both reporting years, the database contains comparable and stable numbers of in-

dividuals at risk for severe COVID-19. In both cohorts, the most common risk factors for severe COVID-19 identified were older age (≥60 years) and cardiovascular disease, which were present in about one-third of individuals in the SHI (Table 1).

Nirmatrelvir/ritonavir is contraindicated for patients with severe renal impairment or severe hepatic impairment.[25] In Analysis 1, the extrapolated number of individuals in the SHI population with contraindications for nirmatrelvir/ritonavir therapy due to severe liver or kidney disease in 2018 and 2019 was 658,363 (1.93%) and 679,800 (1.98%), respectively. Most individuals in this group were diagnosed with CKD (stage 4, 5 or unspecified) (Table 2).

In Analysis 2, the extrapolated number of individuals in the SHI population at risk for severe COVID-19 with pDDIs under ritonavir-containing therapy was approximately 19 million according to the nirmatrelvir/ritonavir SmPC, with a prevalence of about 56%: 18,859,374 (55.38% of total SHI population) in 2018 and 19,285,464 (56.05%) in 2019. Most individuals with pDDIs were identified by a nirmatrelvir/ritonavir SmPC-based physician's decision: 13,357,384 (39.22%) in 2018 and 14,033,596 (40.78%) in 2019. The number of patients with contraindications due to comedications was 5,501,990 (16.16%) in 2018 and 5,251,868 (15.26%) in 2019. According to the list published by Mikus et al.,[27] 15 million individuals were at risk for pDDIs, with a prevalence of 44%: 14,941,639 (43.88%) in 2018 and 15,242,775 (44.30%) in 2019 (Figure 2 and Supplementary Material 4). Most individuals received comedications contraindicated for a ritonavir-containing COVID-19 therapy: 10,740,177 (31.54%) in 2018 and 10,745,092 (31.23%) in 2019. The number of individuals receiving comedication requiring a physician's decision in the case of ritonavir-containing COVID-19 therapy was 4,201,462 (12.34%) in 2018 and 4,497,683 (13.07%) in 2019.

A unified analysis of both approaches estimated that nearly 6 million individuals in the SHI population, with a prevalence of about 17%, had contraindications with ritonavir-containing therapy according to the nirmatrelvir/ritonavir SmPC: 5,917,451 (17.38%) in 2018 and 5,693,328 (16.55%) in 2019. Contraindications due to persisting

Table 1. Individuals with risk factors for severe COVID-19 in the German Analysis Database for Evaluation and Health Services Research (DADB) and extrapolated Statutory Health Insurance (SHI) system in 2018 and 2019.

Risk factor	2018			2019		
	DADB (*n*=2,444,492)	SHI (*n*=60,896,812)	Proportion of SHI (%)	DADB (*n*=2,470,018)	SHI (*n*=60,994,083)	Proportion of SHI (%)
	n			*n*		
Age ≥60 years	651,622	20,031,019	32.89	680,734	20,329,940	33.33
Chronic liver disease	132,710	3,541,354	5.82	137,217	3,603,863	5.91
Chronic kidney disease	83,492	2,671,245	4.39	88,412	2,768,375	4.54
Chronic lung disease	240,128	6,314,195	10.37	247,560	6,420,698	10.53
Cardiovascular disease	733,664	20,376,755	33.46	753,445	20,538,439	33.67
Cancer	113,126	3,266,319	5.36	118,401	3,353,428	5.50
Diabetes	221,424	6,363,048	10.45	227,946	6,411,993	10.51
Down syndrome	752	17,680	0.03	785	18,466	0.03
Neurological and psychiatric disease	408,413	10,649,992	17.49	425,588	10,944,787	17.94
Obesity	232,828	6,023,589	9.89	242,792	6,189,256	10.15
Compromised immune system[a]	93,196	2,464,990	4.05	97,640	2,546,370	4.17

[a]Compromised immune system is defined by ICD-10-GM[28] and shown in the Supplementary Material: B20, B21, B22, B23, B24, D70, D71, D72, D73, D74, D75, D76, D77, D80, D81, D82, D83, D84, D86, D89, D90, K50, K51, M05, M06, O98.7, Z09.80, Z94

Figure 2. Proportion of individuals at risk for severe COVID-19 in 2019 who have contraindications for ritonavir-containing treatment or may develop ritonavir-CYP3A4-mediated pDDI requiring a physician's decision (Analysis 2).

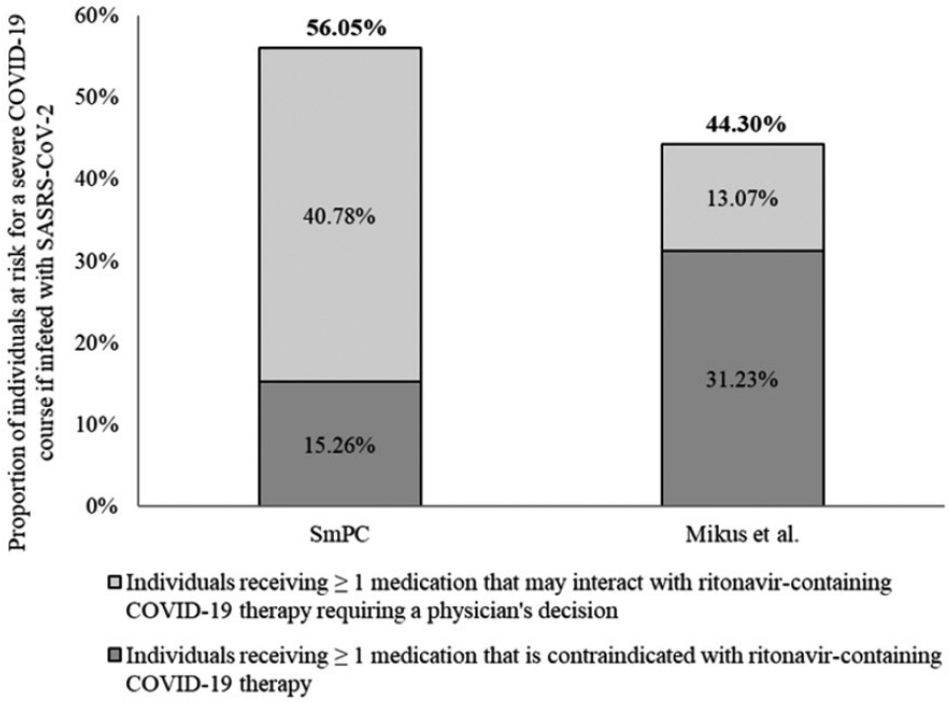


Table 2. Individuals with risk factors for severe COVID-19 and with severe liver or kidney disease in the German Analysis Database for Evaluation and Health Services Research (DADB) and extrapolated Statutory Health Insurance (SHI) system in 2018 and 2019.

ICD-10-GM	Description	2018			2019		
		DADB	SHI	Proportion of SHI (%)	DADB	SHI	Proportion of SHI (%)
		n			*n*		
K72.0	Acute and subacute hepatic failure	133	3466	0.01	127	3273	0.01
K74.72[a]	Cirrhosis of liver, Child-Pugh score C	–	–	–	124	2938	0.01
N18.4	Chronic kidney disease, stage 4	6470	221,932	0.65	7024	235,136	0.68
N18.5	Chronic kidney disease, stage 5	3699	108,958	0.32	3831	110,380	0.32
N18.9	Chronic kidney disease, unspecified	13,692	442,983	1.30	14,211	449,863	1.31

[a]K74.72 was introduced with ICD-10-GM version 2019.

comorbidities such as severe kidney or liver disease (Analysis 1) and contraindications according to the list published by Mikus et al.[27] were analysed for nearly 11 million individuals with a prevalence of about 32%: 10,949,133 (32.15%) in 2018 and 10,957,509 (31.84%) in 2019 (Supplementary Material 4).

Discussion

This study included adults with one or more risk factors for severe COVID-19 for two reporting years, 2018 and 2019, who were selected to represent fully the at-risk population. The study population included individuals covered by SHI and who met continuous eligibility criteria. In Germany, approximately 88% of the population are covered by SHI.[37] The analysis was performed by extrapolation from the DADB, which is a representative sample of the German SHI population. The number of fully insured individuals was stable within the DADB and, by extrapolation, within the SHI population over both reporting years. The calendar years 2020 and 2021 were not included in the analysis because the COVID-19 pandemic, which limited visits to physicians, may have affected claims data and thus bias extrapolation. The prevalence of individuals at risk for severe COVID-19 was calculated based on known risk factors (defined by RKI criteria) and was stable over 2018–2019, that is, approximately 56% of the German SHI population or more than 34 million individuals. A recent study based on a sample of 15,932 participants reported a similar frequency of risk factors for severe COVID-19 (46.0%).[38]

At the time of writing, two oral treatments for COVID-19 were available in Germany – nirmatrelvir/ritonavir, which is authorized for use in the EU,[25] and molnupiravir, for which a marketing authorization application has been submitted.[39] According to the approved label, nirmatrelvir/ritonavir has several contraindications and numerous pDDIs due to inhibition of CYP3A4,[25] which may limit its use in routine clinical practice. In addition, ritonavir inhibits other CYP isoenzymes. However, those are considered minor and are deemed of low clinical relevance.[40] Although pDDIs are not necessarily a contraindication for ritonavir-containing therapy, the attending physician is required to decide on the course of action. None of the oral antiviral treatment options is indicated for pregnant and breastfeeding women; consequently, these women were excluded from the base cohort for subsequent analyses.

The proportion of individuals at risk for severe COVID-19 with contraindications for nirmatrelvir/ritonavir therapy due to severe liver or kidney disease was of ~2%. As individuals with these conditions are at high risk for severe COVID-19, the availability of alternative treatment options, such as remdesivir or monoclonal antibodies (dependent on the currently dominant strain of SARS-CoV-2), are of particular benefit for this group and should be considered by the physician. However, nirmatrelvir/ritonavir is currently the only available oral therapy against COVID-19 approved by the EMA.[11] In cases where coadministration of nirmatrelvir/ritonavir with other drugs is contraindicated, there are three options: either pause the drug(s), replace the drug(s), or consider other antiviral treatment options for early COVID-19 such as molnupiravir.

The prevalence of individuals with a prescription for one or more medications with pDDIs with ritonavir-containing COVID-19 treatment (as described by Mikus et al.[27]) was about 56% of the base cohort (individuals at risk for severe COVID-19), equating to approximately 19 million individuals in the SHI population.

Most individuals (approximately 40%) with pDDIs were identified by a nirmatrelvir/ritonavir SmPC-based physician's decision. In comparison, based on the list published by Mikus et al.,[27] 44% of the base cohort were at risk of pDDIs, equating to approximately 15 million individuals. Nearly one-third had contraindications for a ritonavir-containing COVID-19 therapy. Both sets of figures were calculated based on active pharmaceutical ingredients listed in the nirmatrelvir/ritonavir SmPC[25] and in the publication of Mikus et al.[27] These authors listed and classified drugs with pDDIs with nirmatrelvir/ritonavir by recommendations for action. The list represents drugs that are routinely used in clinical practice in Germany.[41] In addition, the COVRIIN guideline on DDI management with nirmatrelvir/ritonavir provides a list of the most important medications frequently used in Germany triggering contraindications.[42] This list includes cardiac agents such as antiarrhythmics (amiodarone, flecainide), heart failure medications (ivabradine), diuretics (eplerenone), statins (simvastatin), antiplatelet agents (clopidogrel, ticagrelor) and anticoagulants (rivaroxaban); pulmonary arterial hypertension drugs (bosentan, sildenafil), antirheumatic drugs (colchicine); urological drugs such as α-blockers (alfuzosin) and erectile dysfunction agents (sildenafil, tadalafil, vardenafil); antibiotics (rifampicin) and antivirals (glecaprevir/pibrentasvir); neurological medications such as antiepileptic and sedative drugs (phenytoin, phenobarbital, carbamazepine, diazepam, estazolam, flurazepam, midazolam, clorazepate, triazolam); antipsychotics (clozapine, quetiapine); migraine treatment (ergotamine); oncology chemotherapeutics and antineoplastic drugs (neratinib, venetoclax, apalutamide); analgesics (pethidine, norpethidine, piroxicam, propoxyphene); and antihistamines (astemizole, terfenadine).[42] According to STIKO guidelines, a relevant reduction of vaccination efficacy should be anticipated

amongst patients undergoing antineoplastic therapy, patients with (congenital) innate immune defects and patients following stem-cell or organ transplantation.[43] The latter receive immunosuppressive medications such as cyclosporin, tacrolimus or everolimus, which are contraindicated with ritonavir-containing COVID-19 therapy. Whilst iatrogenic immunosuppression renders those patients especially prone to severe courses of COVID-19 with no efficient protection by vaccination possible, their treatment with oral ritonavir-containing therapy is extremely challenging and should only be considered under close examination of drug levels and potential adverse events preferably under stationary conditions. The high medical need for COVID-19 antiviral treatment in these patients is supported by the fact that, though concomitant administration of calcineurin inhibitors and nirmatrelvir/ritonavir is contraindicated, some patients report their experience with managing DDIs between those substances. From our own clinical experience, concomitant administration of nirmatrelvir/ritonavir and tacrolimus in at least one case resulted in sudden high levels of tacrolimus and persistent symptoms of COVID-19, leading to treatment interruption and acute renal injury. Others reported that tacrolimus should be paused during nirmatrelvir/ritonavir treatment and resumed at reduced doses after completion of antiviral treatment.[44] This resulted in therapeutic or supratherapeutic levels of tacrolimus during nirmatrelvir/ritonavir treatment despite discontinuation of tacrolimus. Resumption of tacrolimus treatment is also challenging, and some patients were found to have subtherapeutic levels of tacrolimus after nirmatrelvir/ritonavir discontinuation.[45]

Recommendations for 5 of the 190 drugs or drug combinations listed by Mikus et al.[27] differed from those made by the EMA.[27]

Finally, unified analysis combining individuals with comorbidities in whom nirmatrelvir/ritonavir is contraindicated, that is, those with severe kidney and liver disease, and contraindicated medications produced a prevalence of 17% according to the nirmatrelvir/ritonavir SmPC (Group 1 + Group 2) and 32% derived from the list published by Mikus et al.[27] (Group 1 + Group 3), representing 6 and 11 million individuals in the SHI population, respectively.

A retrospective observational study design using secondary SHI claims data has several limitations. It should be noted that SHI claims data are collected for the processing of payments rather than to conduct pharmaco-epidemiological research. A common limitation of retrospective analyses with German claims data is the unavailability of detailed clinical data, for example, disease activity, disease severity, symptom scores, clinical test results, quality of life data, and documentation of prescribed doses.[46] Furthermore, the presence of a diagnostic code on a medical claim does not constitute definite proof for the presence of the corresponding disease. This was addressed by application of the M2Q criterion for outpatient diagnoses or a confirmed inpatient diagnosis. Misclassification bias may arise from incorrect assignment of the diagnostic code and use of a diagnostic code as an exclusion criterion for a disease. ATC codes were used to query pDDIs but these were not available for claims from inpatient data. Pharmacy claims data may not include all prescribed comedication drugs as, for example, samples received at a physician's office or in hospitals will not be recorded as a claim. Furthermore, over-the-counter drugs that lead to pDDIs (e.g. St. John's Wort) are not available in SHI claims data.

As this study analysed data from 2018 to 2019, individuals included in the study were unvaccinated for COVID-19, which does not reflect the present situation (mid-December 2022) in Germany, where 63.5 million people (76.3% of the population) have received at least basic COVID-19 immunization, whilst 62.6% had at least one booster vaccination. In particular, the vaccination rate amongst the ≥60-year-old age group can be considered highly vaccinated, with 85.4% receiving at least one booster vaccination.[47] In addition, based on seroprevalence studies like SeBluCo,[48] it can be assumed that, by mid-2022, almost every German would have built up sufficient vaccine immunity and/or would have been exposed to SARS-CoV-2, thus enhancing hybrid immunity. This was confirmed by a recent study that analysed blood samples from 15,932 adult German participants for the presence of antibodies against the S-antigen and N-antigen of the SARS-CoV-2 virus: 95.7% and 44.4% had antibodies against the S-antigen and N-antigen, respectively.[38] Amongst the most vulnerable age groups (those aged >65 years and >80 years), the presence of anti-S-antibodies was 97.4% and 98.8%, respectively, and the presence of anti-N-antibodies in those aged >80 years was 28.5%. Consequently, the risk for developing severe COVID-19 has decreased, though the RKI has not modified its criteria for high risk of severe COVID-19.[34] It is worth mentioning that German treatment guidelines recommend individual assessment of the risk for a severe course of COVID-19 treatment.[49] According to these recommendations, antiviral treatment for COVID-19 should be considered especially for patients with immunodeficiency/immunosuppression, elderly, and patients with severe comorbidities and incomplete immunization. Due to the high immunity of the German population, the number of individuals with an indication for antiviral treatment according to German guidelines is substantially lower than our analyses based on RKI criteria. However, within the immunocompromised, comorbid population that cannot be immunized efficiently

and is still at risk for severe COVID-19, the proportion of patients who might face pDDIs upon treatment with ritonavir-containing COVID-19 treatment might be even higher than estimated in our analyses reported herein. Extrapolation from the DADB was adjusted for age and sex, but regional distribution was not considered. Furthermore, not all healthcare insurers, especially private healthcare insurers, were included in the database, which introduces selection bias. To compensate for this, BAS data were used to determine an age-specific and sex-specific factor that was used to extrapolate DADB data. As this study determined the prevalence for the whole of Germany, a regional analysis was unnecessary. Furthermore, fluctuation in the database might occur due to individuals changing healthcare service provider. However, these individuals were excluded from the analysis and represent <1% of individuals in the DADB, which is considered stable over successive years.

Conclusions

Within the limitations of the study design, this analysis of 2018 and 2019 insurance claims data found that more than half (about 56%) of the German adult SHI population might be at risk for severe COVID-19, depending on their immune status. Our analysis suggests that administering ritonavir-containing COVID-19 therapy to at least one-third of individuals at risk for severe COVID-19 can be challenging in clinical practice as patients need to be fully informed about concomitant diseases and therapies, and a thorough medical record review and close monitoring are required. In some cases, ritonavir-containing treatment may not be appropriate due to contraindications, risk of pDDIs, or both. For those individuals, an alternative ritonavir-free treatment should be considered.

Data availability

The datasets used and/or analyzed during the current study are available on request. The MSD data-sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request.

Prior presentation

Parts of this paper were accepted for presentation in March 2023 with the poster title 'Prevalence of individuals with risk for severe COVID-19 in whom ritonavir-containing therapies are contraindicated or may lead to interactions with concomitant medications (80496)' at the 11th German-Austrian AIDS Congress (DÖAK) in Bonn, Germany.

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