Figure 4. Network analysis between risk factors for immunocompromise.

Table 1.   Clinical and Severity Characteristics of the 2 Study Groups (Immunocompetent vs Immunocompromised)

	Patients, No. (%)[a]		
Variable	Immunocompetent (n = 3050)	Immunocompromised (n = 652)	P Value
Age, median (IQR)	69 (54–81)	65 (52–74)	<.001
Underweight	125 (6.5)	41 (10.5)	.004
Malnutrition	243 (8.0)	80 (12.3)	<.001
Bedridden	355 (11.6)	60 (9.2)	.04
Chronic aspiration	224 (7.3)	33 (5.1)	.02
Bronchiectasis	136 (4.5)	42 (6.4)	.03
Severe COPD	72 (2.4)	28 (4.3)	.006
Interstitial lung disease	60 (2.0)	35 (5.4)	<.001
Lung transplantation	0 (0.0)	7 (1.1)	<.001
Tracheostomy	37 (1.2)	16 (2.5)	.02
Hypertension	1401 (45.9)	254 (39.0)	.001
Liver disease	103 (3.4)	37 (5.7)	.005
Cirrhosis	50 (1.6)	20 (3.1)	.02
Dementia	372 (12.2)	36 (5.5)	<.001
Enteral tube feeding	36 (1.2)	16 (2.5)	.01
Chronic renal failure	315 (10.3)	85 (13.0)	.04
Hemodialysis	34 (1.1)	18 (2.8)	.001
ICS use	462 (15.2)	128 (19.6)	.005
PPI use	777 (25.5)	251 (38.5)	<.001
Indwelling catheter	52 (1.7)	27 (4.1)	<.001
Prior mycobacteria diseases	70 (2.3)	26 (4.0)	.01
Prior ESBL	39 (1.3)	16 (2.5)	.02
Prior *Pseudomonas*	68 (2.2)	33 (5.1)	<.001
Severe CAP	840 (27.5)	190 (29.1)	.41

Abbreviations: CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; ESBL, extended-spectrum β-lactamase; ICS, inhaled corticosteroids; IQR, interquartile range; PPI, proton pump inhibitors.

[a]Data represent No. (%) unless otherwise specified.

Table 2. Pathogens in the 2 Study Groups

	Patients, No. (%)		
Pathogen	Immunocompetent (n = 2626)	Immunocompromised (n = 596)	*P* Value
Pathogens covered by CAP therapy			
Streptococcus pneumoniae	218 (8.3)	50 (8.4)	>.99
Atypical	50 (1.9)	13 (2.2)	.78
Legionella	21 (0.8)	10 (1.7)	.08
MRSA	83 (3.2)	12 (2.0)	.17
MSSA	73 (2.8)	20 (3.4)	.53
Pseudomonas aeruginosa	98 (3.7)	35 (5.9)	.02
Haemophilus influenzae	65 (2.5)	10 (1.7)	.31
Klebsiella pneumoniae	89 (3.4)	22 (3.7)	.81
Influenza virus	126 (4.8)	28 (4.7)	>.99
Pathogens not covered by CAP therapy			
Non-CAP bacteria			
Acinetobacter baumanii	33 (1.3)	7 (1.2)	>.99
Nocardia spp.	0 (0.0)	4 (0.7)	<.001
Mycobacteria			
Mycobacterium tuberculosis	21 (0.8)	5 (0.8)	>.99
NTM	2 (0.1)	5 (0.8)	.002
Fungi			
Aspergillus fumigatus	10 (0.4)	8 (1.3)	.01
Actinomyces	2 (0.1)	0 (0.0)	>.99
Cryptococcus	3 (0.1)	0 (0.0)	.94
Pneumocystis jirovecii	5 (0.2)	13 (2.2)	<.001
Viruses			
Adenovirus	5 (0.2)	0 (0.0)	.62
Coronavirus	3 (0.1)	3 (0.5)	.047
Metapneumovirus	3 (0.1)	2 (0.3)	.51
RSV	7 (0.3)	6 (1.0)	.03
MDR pathogens	231 (8.8)	54 (9.0)	.54

Abbreviations: CAP, community-acquired pneumonia; MDR multidrug-resistant; MRSA methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *S. aureus*; NTM, nontuberculous mycobacteria; RSV, respiratory syncitial virus.

patients; *P* < .001), nontuberculous mycobacteria (NTM) (5 [0.8%] vs 2 [0.1%]; *P* < .002), *A. fumigatus* (8 [1.3%] vs 10 [0.4%]; *P* < .01), *P. jirovecii* (12 [2.0%] vs 5 [0.2%]; *P* < .02), and viruses, such as coronavirus (3 [0.5%] vs 3 [0.1%]; *P* < .047), and respiratory syncytial virus (6 [1.0%] vs 7 [0.3%]; *P* < .03).

Table 3. Multivariable Logistic Regression Analysis

	OR (CI 95%)				
Variable	*Pseudomonas aeruginosa*	Non-CAP Bacteria	Fungi	*Mycobacterium tuberculosis*	Virus Other Than Influenza
Severe COPD	2.89 (1.34–6.22)	…	…	…	…
Tracheostomy	6.95 (2.87–16.85)	2.91 (1.01–8.38)	…	…	…
ICS use	1.76 (1.09–2.82)	…	…	…	…
Indwelling catheter	2.49 (1.02–6.06)	…	…	…	…
Prior *Pseudomonas*	19.20 (11.71–31.50)	…	…	…	…
COPD	…	1.78 (1.07–2.99)	…	…	…
Severe CAP	…	2.36 (1.42–3.93)	…	…	2.56 (1.27–5.19)
AIDS	…	…	15.10 (6.36–35.88)	…	…
Hematological cancer	…	…	4.65 (1.85–11.69)	…	5.49 (2.20–13.70)
Malnutrition	…	…	…	5.14 (2.21–11.93)	…

Blank cells indicate no statistical significancy.

Abbreviations: CAP community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; OR, odds ratio.

Once adjusted for confounders, no risk factors of immunocompromise have been recognized for *P. aeruginosa* infection. Likewise, pathogens not covered by usual CAP therapy were found to be associated not with immunocompromise but with chronic obstructive pulmonary disease (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.07–2.99; *P* = .03), tracheostomy (2.91; 1.01–8.38; *P* = .048), and severe pneumonia (2.36; 1.42–3.93; *P* = .001) (Table 3).

Results showed that AIDS (OR, 15.10; 95% CI, 6.36–35.88; *P* ≤ .001) and hematological cancer (4.65; 91.85–11.69; *P* = .001) were independently associated with fungal infections; hematological cancer (5.49; 2.20–13.70; *P* < .001) and severe pneumonia (2.56; 1.27–5.19; *P* = .009) with infection by viruses other than influenza; and AIDS (4.41; 1.53–12.73; *P* = .006) and malnutrition (4.50; 2.08–9.72; *P* < .001) with mycobacterial infections. An additional analysis was conducted on mycobacteria, including *M. tuberculosis* and NTM. At multivariable analysis, *M. tuberculosis* was independently associated with malnutrition only (OR, 5.14; 95% CI, 2.21–11.93; *P* < .001). At univariate analysis, patients with AIDS were at higher risk for NTM (23.06; 4.39–121.12; *P* < .001).

A subanalysis was conducted among patients with chronic steroid use versus other risk factors for immunocompromise. Patients with chronic steroid use seemed to be more frequently affected by bacteria not covered by standard CAP therapy (10 [3.4%] vs 1 [0.3%] patients; *P* = .002), *Nocardia* spp. in particular (4 [0.4%] vs 0 [0.0%]; *P* = .03). No differences in the severity of the disease were found (see Supplementary Table 5).

DISCUSSION

The main findings of the present study are as follows: (1) 17.6% of patients admitted with pneumonia from the community have ≥1 risk factor for immunocompromise, with significant differences among continents and countries (ranging from 15.4% to 24.8% by continent and from 80.0% to 4.1% by country); (2) chronic steroid use is by far the most prevalent risk factor leading to immunocompromise, followed by hematological cancer and chemotherapy; (3) 1 of 2 immunocompromised patients has an overlap of ≥2 risk factors, which are also associated between one another in different ways; and (4) the 2 risk factors for immunocompromise independently associated with specific pathogens are AIDS (ie, fungal and mycobacterial infections) and hematological cancer (ie, fungal infection and viral infections other than influenza).

Almost 1 in 5 hospitalized patients with CAP are not immunocompetent. Therefore, it is mandatory to provide clinicians with recommendations or guidelines for the management of hospitalized patients with pneumonia coming from the community who have risk factors for immunocompromise. Currently, there are no guidelines for assessing pneumonia in immunocompromised patients coming from the community.

Randomized controlled trials (RCTs) and observational prospective studies are missing owing to the fact that, generally, studies assessing management strategies for pneumonia exclude immunocompromised patients or take into account only a single specific risk factor [12–21]. This lack of information about immunocompromise could lead to both underestimation of the real prevalence with a higher rate of treatment failure and to overestimation and overuse of wide-spectrum antibiotics.

We found a 17.6% global prevalence of immunocompromise among patients coming from the community with pneumonia, with a significantly higher frequency in South and North America. This variability among continents and countries is probably attributable to different healthcare systems and rates of hospitalization of immunocompromised patients. Our analysis showed that the most frequent risk factor for immunocompromise is the chronic use of systemic steroids. Aging of the population and therapeutic advancements have favored the increased burden of chronic diseases and long-term therapies with immunosuppressive agents [8, 9]. In particular, steroids are the agents most frequently prescribed, for their wide spectrum of efficacy in several diseases [13, 17, 19]. Therefore, many patients presenting to the emergency room with pneumonia are receiving chronic steroid treatment. No data are available on this population group, and further studies are needed to characterize these patients and provide individualized management.

Hematological cancer and chemotherapy were other leading immunocompromised factors. These findings are consistent with those in previous studies; patients recruited in observational studies include patients with solid or hematological cancer and those who underwent chemotherapy with associated neutropenia [15–20, 22]. Dedicated guidelines and recommendations are available, especially on respiratory viruses, fungi, and *P. jirovecii* [23–26].

Our network analysis showed that several risk factors for immunocompromise show associations, especially chemotherapy, associated with hematological cancer and solid tumor, and other immunocompromise, associated with chronic steroid use. Moreover, neutropenic patients are well represented and mainly affected also by hematological cancer or under treatment with chemotherapy. Our results suggest that patients may have >1 risk factor characteristic and clinical assessment should be comprehensive, taking into consideration risk factors for immunocompromise and their associated biological mechanisms. In contrast, AIDS, lung transplantation, asplenia, and aplastic anemia seem to be less frequent at admission and to represent distinct clinical entities. Findings of previous studies seem to be in line with our results, with AIDS patients considered as a distinct patient population and with very few observational studies available on asplenia and aplastic anemia [21, 27–31]

In agreement with previous reports, *S. pneumoniae* is the leading microorganism in both immunocompromised and immunocompetent groups [32, 33]. Among pathogens covered by

standard CAP therapy, only *P. aeruginosa* was more frequently isolated in immunocompromised compared with immunocompetent patients. These findings differ from microbiological results of previous studies. Gram-positive bacteria, especially *S. aureus*, were more frequently identified in patients with immunocompromise of different causes [22, 30, 34]. Only Li and coauthors [13] found patients with immunological disorders, treated with systemic steroids and cytotoxic agents, to have a higher incidence of infections caused by gram-negative bacteria, mainly *P. aeruginosa*. This similarity with our findings could be explained by the prevalence of patients exposed to chronic steroids in our cohort.

Among pathogens not covered by standard CAP therapy, immunocompromised patients were more frequently infected by *Nocardia* spp., NTM, *P. jirovecii*, *A. fumigatus*, and viruses other than influenza. Infections by *P. jirovecii* and NTM are frequently identified in patients with AIDS [35]. *P. jirovecii* is also frequent in other types of immunocompromise, such as solid or hematological cancer in patients who underwent chemotherapy [18, 19, 36]. Fungal infections (eg, *Candida* spp. and *A. fumigatus*) are highly incident in neutropenic hematological cancer patients [22, 37]. Viral infections other than influenza, especially respiratory syncytial virus, are more frequent in patients who underwent hematopoietic stem cell or lung transplantation [38, 39]. Conversely, *Nocardia* spp. infections are mainly described in solid organ transplant recipients [40]. These results, consistent with previous findings, suggest the need for a more in-depth microbiological workup, including community-acquired pathogens and microorganisms not covered by standard therapy.

Surprisingly, we found that risk factors for immunocompromise were not independently associated with *P. aeruginosa* or non–community-acquired bacteria; in contrast, AIDS and hematological cancer are both associated with fungal, mycobacterial, and noninfluenza viral pneumonia, respectively. Empirical therapy should include *P. aeruginosa* coverage, which is highly prevalent in immunocompromised patients. On the contrary, particular attention should be given to fungal, mycobacterial, and viral causes should be for patients admitted with AIDS and hematological cancer [21–29].

Finally, bacteremia rates did not differ between study groups. To our knowledge, there are no studies on bacteremia and immunocompromise in general. The majority of studies have focused on bacteremia in hematopoietic stem cell transplantation, with prevalences varying from 6% to 44% depending on the type of bacteria and host-related factors [41–43]. Few studies addressed this topic in kidney transplant recipients, reporting a prevalence of bacteremia ranging from 25% to 69% [44, 45]. Finally, few studies have addressed HIV and bacteremia, with prevalences ranging from 10% to 25%, depending on the pathogen and grade of immunosuppression [46, 47]. The prevalence of bacteremia in our study was 5T–6% in both immunocompetent and immunocompromised patients. Differences in the prevalence of bacteremia are due mainly to differences between the risk factors for immunocompromise in our study (chronic steroid use, hematological cancer, and chemotherapy) and those previously reported in the literature.

The current study has both limitations and strengths. First of all, to our knowledge, this is the first study showing a worldwide perspective on immunocompromise among patients coming from the community with pneumonia, with a large and diverse sample of patients enrolled across different countries in 6 continents. However, we were not able to involve many investigators from Asia and Africa, and most cases occurred in North America and Europe, thus limiting the generalizability of our findings. Another major limitation is the unfeasibility of grading the severity of immunocompromise and, therefore, stratifying patients and defining the physiopathological interaction between different risk factors, especially with regard to the use of biological drugs and chronic steroids. Furthermore, potentially important risk factors for an immunocompromised state, such as solid organ transplants other than lung, have not been specifically investigated. Finally, no outcome data have been collected, and this strongly limits our speculations as to the correct empiric antibiotic therapy for use in immunocompromised patients with CAP.

In conclusion, our study offers to the scientific community a perspective on immunocompromised patients coming from the community with pneumonia. Future prospective studies on patients with specific risk factors for immunocompromise could provide practical recommendations. In particular, it will be crucial to prepare guidelines on certain prevalent population groups, such as patients exposed to chronic steroids and those with hematological cancer.

Supplementary Data

Notes