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KLİNİK ÇALIŞMA
RESEARCH ARTICLE

Clinical characteristics and outcome of healthcare associated pneumonia in Turkey

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SUMMARY

Clinical characteristics and outcome of healthcare associated pneumonia in Turkey

Introduction: *Pneumonia in cases with preceding hospitalization, hemodialysis, intravenous therapy, wound care, or chemotherapy within the prior 30 days and residence in nursing homes are defined as healthcare associated pneumonia (HCAP). The aim of this study was to compare the demographic and laboratory data, isolated causative agents and prognosis of patients with community-acquired pneumonia (CAP) and HCAP in a large population in Turkey.*

Materials and Methods: *The data of 785 cases (average age 65.3 ± 16.4, 530 male) registered to Turkish Thoracic Society Respiratory Infections Study Group CAP database (TURCAP) were examined. The demographic data, clinical history, pneumonia severity scores (PSI), laboratory and radiologic findings of the CAP and HCAP patients were compared.*

Results: *Out of 785 cases, 207 (26.4%) were diagnosed with HCAP and 578 (73.6%) with CAP. Among HCAP cases, 140/207 (67.6%) had preceding hospitalization in the last 90 days, 28/207 (13.5%) were on a hemodialysis program during the previous 30 days and 22/207 (10.6%) were staying in nursing homes. Patients with HCAP more frequently had comorbidities (93.2% vs. 81.6%; p= 0.001) and higher PSI scores (103.9 ± 37.2 vs. 94.6 ± 35.4; p= 0.002) compared to patients with CAP. A causative microorganism was isolated in only 12.1% (70/578) of CAP and 14.5% (30/207) of HCAP patients. The length of stay in hospital was higher in HCAP than CAP (8.6 ± 5.5 vs. 7.5 ± 6.1 days, p= 0.03); however the rates of treatment failure, intensive care unit admission and mortality were similar.*

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Conclusion: *In comparison to CAP, HCAP patients tend to have more severe disease, despite have no difference in mortality. The current criteria for HCAP do not predict worse clinical outcomes. Further work is required to define local risk factors for multidrug-resistant pathogens.*

Key words: *Healthcare associated pneumonia, community acquired pneumonia, pneumonia severity index*

ÖZET

Türkiye'de sağlık bakımı ile ilişkili pnömoni olgularının klinik özellikleri ve sonuçları

Giriş: *Hastaneye yatış, hemodiyaliz programında bulunma, sağlık bakım evlerinde yaşama, önceki 30 günde evde yara bakımı öyküsü, ayaktan intravenöz tedavi ve kemoterapi öyküsü olan olgularda toplumda gelişen pnömoniler, sağlık bakımı ilişkili pnömoni (SBİP) olarak adlandırılmaktadır. Türkiye'de geniş bir popülasyonu kapsayan çalışmamızda, hastanede yatan toplumda gelişen pnömoni (TGP) ve SBİP olgularının başvuru özelliklerinin, laboratuvar verilerinin, etken dağılımlarının ve prognozlarının karşılaştırılması amaçlanmıştır.*

Materyal ve Metod: *Türk Toraks Derneği Solunum Sistemi İnfeksiyonları Çalışma Grubu Pnömoni Veri Tabanı (TURCAP)'na yedi merkez tarafından kayıt edilmiş olan 785 (ortalama yaş 65.3 ± 16.4, 530 erkek) TGP ve SBİP olguları değerlendirilmiştir. Demografik özellikler, klinik öykü, pnömoni ağırlık skorları, laboratuvar ve radyolojik bulgular karşılaştırılmıştır.*

Bulgular: *785 olguda 207 (%26.4)'si SBİP ve 578 (%73.6)'i TGP tanısı almıştır. 207 SBİP olgusunun 140 (%67.6)'ının son 90 günde hastaneye yatış öyküsü olduğu, 28 (%3.6)'inin son 30 günde hemodiyaliz programına alındığı ve 22 (%10.6)'sinin sağlık bakım evinde kaldığı saptanmıştır. SBİP olgularında TGP'ye kıyasla komorbidite sıklığı artmış (%93.2'ye karşın %81.6; p= 0.001); PSI skoru yüksek (103.9 ± 37.2'ye karşın 94.6 ± 35.4; p= 0.002) saptanmıştır. Etken izolasyonu TGP'de %12.1 (70/578), SBİP'te %14.5 (30/207) oranında sağlanabilmiştir. Hastanede yatış süresi SBİP olgularında daha yüksek bulunmakla beraber (sırasıyla 8.6 ± 5.5'e karşın 7.5 ± 6.1 gün, p= 0.03); tedavi başarısı, yoğun bakımda kalış ve mortalite oranları açısından farklılık saptanmamıştır.*

Sonuç: *TGP'ye kıyasla SBİP olgularında hastalık daha ağır seyretmekle beraber mortalitede fark izlenmemektedir. SBİP için mevcut kriterler olumsuz klinik sonuçları tahmin etmemektedir. Çok ilaca dirençli patojenlere yönelik lokal risk faktörleri tanımlayabilecek çalışmalara gereksinim vardır.*

Anahtar kelimeler: *Sağlık bakımı ilişkili pnömoni, toplumda gelişen pnömoni, pnömoni ağırlık indeksi*

INTRODUCTION

Healthcare-associated pneumonia (HCAP) has originally been defined as pneumonia that develops in patients who wereadmitted to an acute-care hospital for two or more days within the preceding 90 days, reside in a nursing home or long-term care facility, received intravenous antibiotic therapy, chemotherapy, or wound care within the preceding 30 days or were on a hemodialysis program (1,2). This has been associated with a higher frequency of drug-resistant organisms, and consequently, with worse outcomes. (1-6). However, this definition has recently been challenged with several studies that showed that other risk factors better predicted the probability of drug-resistant pathogens (7-10). Besides, a Spanish study involving 34 intensive care units (ICU) found thatin patients meeting the original definition of HCAP, the frequency of resistant pathogens and mortality rates were similar to patients with community-acquired pneumonia (CAP) (11). Moreover, guideline-based antibiotic treatment did not improve outcomes in HCAP (12).

Patient populations, healthcare policies and risk factors for drug resistance may vary among countries and these differences may account for some of the discrepencies found in HCAP studies. There is no data in Turkey, regarding HCAP and how it differs from CAP. The aim of this study was thus to compare the demographic and laboratory data, causative agents and prognosis in patients with CAP and HCAP in a large population of patients admitted to four university hospitals.

MATERIALS and METHODS

The data from all patients with CAP registered to Turkish Thoracic Society CAP database (TURCAP) by four university hospitals from September 2009 to September 2013 were analyzed. Briefly, this is a web-based database, where several tertiary care centers prospectively register relevant clinical data of their patients diagnosed with community-acquired pneumonia. The project is supported with a grant from the Turkish Thoracic Society. Nonimmuncompromised patients older than 18 years with the presence of a new radiographic infiltrate and at least two compatible clinical symptoms were included in the study. Cases with at least one of the risk factors listed below were defined as HCAP and the remaining patients as CAP (6):

- Hospitalization for 2 days or more in the preceding 90 days

- Residence in a nursing home or extended care facility
- Home infusion therapy (including antibiotics)
- Chronic dialysis within 30 days
- Home wound care

The database did not include any information on the presence of multidrug-resistant pathogens in family members.

The demographic data (age, gender, smoking history, comorbidities), laboratory findings including C-reactive protein (CRP), procalcitonin, arterial blood gases, culture results and radiologic findings of the two groups were compared. The initial risk class was assessed according to CURB-65 and Pneumonia Severity Index (PSI) scores (13,14). The length of stay in the hospital and in the ICU, need for ICU admission, treatment response and mortality rates were compared to evaluate the prognosis.

The data were analyzed for risk factors for pneumonia due to drug-resistant pathogens. These included *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacteriaceae* producing extended-spectrum beta-lactamases and methicillin-resistant *Staphylococcus aureus*. Thus, comparisons were made for relevant clinical and laboratory parameters between patients infected with these bacteria and with bacteria that are known to be susceptible to empiric antibiotic treatment.

Patients with missing data were excluded. The study was approved by the local ethics committee.

Statistical Analysis

SPSS Statistical Software was used for statistical analysis. T-test and chi-square test were used to examine between group analysis. Linear multivariate regression analysis was used for examining independent variables.

RESULTS

A total of 790 patients were recorded in the TURCAP database. Of these, five were not included in this study, because crucial data for this particular analysis were missing. Thus, 785 patients (530 male, average age 65.3 ± 16.4) were examined. Of these, 207 (26.4%) met the diagnostic criteria for HCAP and 578 (73.6%) had CAP. Among HCAP patients, 140 (17.8%) had been hospitalized in the preceding 90 days, 28 (3.6%) were on a hemodialysis program and 22 (2.8%) resided in nursing homes.The remaining 17 patients either received infusion therapy or wound care at home.

The demographic features of HCAP and CAP patients were similar, except that a higher proportion of HCAP patients had comorbidities (93.2% vs 81.6%; p= 0.001) (Table 1). The Pneumonia Severity Index was higher in HCAP patients (103.9 ± 37.2 vs 94.6 ± 35.4, p= 0.002). The relevant laboratory findings in the two groups are shown in Table 1. Briefly, there was no difference in the levels of inflammatory markers; i.e. CRP and procalcitonin, HCAP patients had worse renal function, but the mean PaO_2 level was somewhat lower in the CAP group.

Table 1. Demographic, clinical and laboratory findings of the study population at admission

	HCAP (n= 207)	CAP (n= 578)	P
Age	66.3 ± 15.8	64.9 ± 16.6	0.29
Gender (male), n (%)	147 (71.0)	383 (66.3)	0.23
Presence of comorbidity, n (%)	193 (93.2)	472 (81.6)	0.01
Smoking history (pack-years)	38.6 ± 23.7	40.5 ± 28.6	0.51
PSI score	103.9 ± 37.2	94.6 ± 35.4	0.01
CURB-65 score	2.23 ± 1.1	2.12 ± 0.9	0.21
Leucocyte count (cell/mm^3)	12703 ± 5773	13564 ± 6784	0.11
CRP (mg/dL)	15.0 ± 12.1	16.0 ± 13.5	0.23
Procalcitonin (ng/mL)	7.7 ± 16.8	4.2 ± 9.9	0.34
Albumin (g/dL)	3.5 ± 3.1	3.3 ± 0.7	0.27
Creatinine (mg/dL)	1.29 ± 1.0	1.01 ± 0.5	< 0.01
PaO_2 (mmHg)	62.2 ± 13.7	58.9 ± 13.3	0.01
$PaCO_2$ (mmHg)	37.2 ± 10.1	36.3 ± 11.9	0.41

PSI: Pneumonia severity index, CRP: C-reactive protein, PaO_2: Partial pressure of oxygen in arterial blood gas, $PaCO_2$: Partial pressure of carbondioxide in arterial blood gas.

Table 2. Isolated pathogens in HCAP and CAP

Isolated microorganisms, n (%)	HCAP (n= 207)	CAP (n= 578)
Streptococcus pneumoniae	4 (1.9)	22(3.8)
Pseudomonas aeruginosa	5 (2.4)	12 (2.1)
Acinetobacter baumannii	4 (1.9)	-
Escherichia coli	3 (1.4)	4 (0.7)
Hemophilus influenzae	3 (1.4)	4 (0.7)
Staphylococcus aureus, met S	4 (1.9)	9 (1.6)
Klebsiella pneumoniae	1 (0.4)	6 (1.0)
Streptococcus (other)	2 (0.9)	1 (0.2)
Moraxella catarhalis	-	3 (0.5)
Others	4 (1.9)	9 (1.6)
Total	30 (14.5)	70 (12.1)

A causative microorganism was isolated in 12.1% (70/578) of CAP and 14.5% (30/207) of HCAP patients. The most frequently isolated causative bacteria were *P. aeruginosa*, *A. baumannii*, *Staphylococcus aureus* (methicillin S) and *S. pneumoniae* in HCAP and *S. pneumoniae* and *P. aeruginosa* in CAP (Table 2).

The length of stay in hospital was higher in HCAP than CAP (8.6 ± 5.5 vs 7.5 ± 6.1 days, p= 0.03). The rate of ICU admission was similar in the two groups (%9.3 vs %9.7, respectively) (p> 0.05). The 30-day mortality rate tended to be higher in HCAP (8.7% vs 5.7%), but the difference did not reach statistical significance (p= 0.14). The initial antibiotic treatment succeeded in 183/207 (88%) of HCAP and 526/578 (91%) of CAP patients (p> 0.05). When the results of in vitro susceptibility tests were examined, appropriate antibiotic treatment was administered to 77.3% and 83.0% of patients with HCAP and CAP, respectively (p= 0.536).

As shown in Table 2, a pathogen was isolated in a total of 100 patients (12.7%). When patients with resistant bacteria (n= 41) were compared with those infected with susceptible bacteria (n= 59), the former was found to have lower serum albumin levels (2.90 ± 0.40 vs 3.24 ± 0.67 respectively, p= 0.016). However, no other differences were identified between patients infected with drug-resistant bacteria and with patients infected with suspectible bacteria including procalcitonin levels and PSI scores (Table 3).

DISCUSSION

This is the first study that evaluated the relevance of the HCAP risk factors in a large population from four different medical centers. HCAP patients were found to have higher PSI scores and were more likely to have comorbidities. They also had a longer time of stay in hospital, but similar risks of ICU admission and of 30-day mortality. Besides, there was no

Table 3. Demographic, clinical and laboratory findings in resistant and susceptible microorganisms isolated groups

	Isolation of resistant microorganisms n= 41	Isolation of susceptible microorganisms n= 59	p value
Age (yrs)	68.8 ± 11.4	66.4 ± 12.7	0.71
Albumin (g/dL)	2.9 ± 0.4	3.3 ± 0.7	0.02
PSI score	112.1 ± 40.7	100.9 ± 32.9	0.30
CRP (mg/dL)	14.3 ± 10.8	13.9 ± 9.5	0.40
Procalcitonin (ng/mL)	12.8 ± 24.7	14.6 ± 21.7	0.79
Gender, male (n, %)	27 (65.9)	37 (62.7)	0.48
COPD (n, %)	18 (43.9)	19 (32.2)	0.07
Cerebrovascular accident (n, %)	5 (12.2)	3 (5.1)	0.07
Renal failure (n, %)	1 (2.4)	2 (3.4)	1.00
Antibiotic use in the last 3 months (n, %)	6 (14.6)	10 (16.9)	1.00
Steroid use in the last 3 months (n, %)	4 (9.8)	5 (8.5)	0.72
Immunosuppressive treatment in the last 3 months (n, %)	1 (2.4)	5 (8.5)	0.40
1-2 lobes involtment in the chest X-Ray	20 (48.8)	23 (39.0)	0.67
> 2 lobes involtment in the chest X-Ray	7 (17.1)	11 (18.6)	0.37

PSI: Pneumonia severity index, CRP: C-reactive protein, COPD: Chronic obstructive pulmonary disease.

difference in the rates of response to the initial empiric antibiotic treatment. Patients infected with multidrug resistant (MDR) pathogens had lower albumin levels compared to those infected with patients with susceptible bacteria.

The concept of HCAP originated from US studies that reported that certain risk factors, which were ultimately included in the definition, were associated with infection due to resistant bacteria and with worse clinical outcomes (15-17). However, this definition has recently been challenged with several studies from Europe and Japan (18-22) and criticized because it led to excessive use of antibiotics, with consequent increases in costs and resistance rates (23-25). Those studies showed that, using the American Thoracic Society definition, etiological agents were similar in CAP and HCAP and defined different risk factors for drug-resistant pneumonia. Importantly, the risk for drug-resistant Gram negative pathogens only increased when three or more risk factors were present (18). A more recent study also showed that HCAP definition alone was not sufficient to predict drug-resistant pulmonary infections and that the predictive power of the currently defined risk factors reaches acceptable levels when they are associated with signs of severe infection, namely the presence of low PaO_2/FiO_2 levels and bilateral infiltrates and/or pleural effusion (26). These are important advances in our understanding of HCAP and are bound to limit the use of broad spectrum antibiotics to a relatively small subgroup of patients.

This study showed that, similarly to the observations in Spain, Japan and Italy, patients who met at least one of the current criteria for HCAP did not have worse clinical outcomes, as compared with CAP patients, except that they had a slightly longer hospital stay. There is thus a need for studies to define local risk factors for drug-resistant pneumonia.

Comparisons were thus made between patients with MDR pathogens and others and the former were found to be more malnourished (with lower serum albumin levels). Low serum albumin levels could also be a marker of more marked inflammatory response in patients with drug-resistant infections. However, the CRP levels and leukocyte counts were similar; the role of inflammation is therefore arguable. Beside hypoalbuminemia, there were no other clinical or laboratory parameter that would predict the presence of a drug-resistant pathogen.

There were two major obstacles to performing a more comprehensive analysis of the data to define risk factors. First, the bacteriologic isolation rate was very low; thus the preliminary findings may not be representative for the general patient population. Second, this was a retrospective analysis of an existing database; thus only the parameters included in the database could be evaluated.

With regards to the low yield of bacteriologic examinations, several potential reasons can be cited: The majority of the patients were still on or had recently been treated with antibiotics prescribed by their primary care physicians. Most of the patients were first admitted to the emergency department, where respiratory samples are rarely obtained prior to the administration of antibiotics. Besides, when a respiratory sample is obtained, the time to reach the microbiology laboratory is variable and may take hours at night shifts or on holidays, when staffing is poor with respect to the patient load. Finally, more sensitive tests using PCR or antigen detection are not routinely done in any of the four participating centers. Thus, the low isolation rate reflects real life and it appears that significant efforts should be made to improve the healthcare processes.

In conclusion, despite its limitations, this study that analyzed prospectively collected data from four tertiary care centers, showed that patients with HCAP risk factors have more severe disease and more comorbidities, but have similar rates of treatment failure, ICU admission and mortality. There is a strong need for better microbiology data, which would allow further work to be done to determine risk factors for MDR pathogens.

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