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Characteristics and Economic Burden of Hospitalized Elderly Patients Due to Community-Acquired Pneumonia

Toplumda Gelişmiş Pnömoni Nedeniyle Hastanede Yatan Yaşlı Hastaların Özellikleri ve Ekonomik Yükü

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Abstract

Objective: The prevalence hospitalization of elderly patients due to community acquired pneumonia (CAP) is high and increases the hospital cost. Characteristics and economic burden of hospitalized elderly patients (>65years) due to CAP were analyzed.

Materials and Methods: We performed a retrospective analysis of the 180 patients who were hospitalized with pneumonia between 01.01.2015-15.11.2017. Patients older than 65 years old and hospitalized for CAP were followed up for up to 30 days from initial hospitalization for mortality and the patients who were discharged were followed up to 90 days of initial hospitalization. Hospital costs were analyzed.

Results: 115(60%) patients were older than 65. 82.4% of the patients received oxygen therapy and 27.8% of them received noninvasive mechanical support. 16.5% of the patients needed intensive care support. PSI was increased with age(p=0.021). Thirty-day mortality was related with older age(p=0.048). Total treatment costs were increased with high PSI (p=0.003). Increased PSI and total cost were significantly associated with mortality (p=0.000). Thirty-day mortality was related with older age(p=0.048), but age was not related with 60-day and 90-day mortality (p=0.244, p=0.469). 30-day mortality was high in patients with COPD and malignancy (p=0.038, p=0.040). No associations were found between total hospital cost and additional diseases (p>0.05).

Conclusion: CAP is a common cause of hospitalization in elderly patients. Older patients had more severe CAP which caused high mortality and high treatment costs; so it is important to identify elderly patients with risk factors for early adequate treatment.

Keywords: Elderly, Hospitalization, Community Acquired Pneumonia, Cost

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Öz

Amaç: Toplum kökenli pnömoni (TKP) nedeniyle yaşlı hastaların hastane yatış sıklığı yüksektir ve hastane maliyetini arttırır. TKP nedeniyle hastanede yatan yaşlı hastaların (>65 yaş) özellikleri ve maliyeti analiz edildi.

Gereç ve Yöntemler: 01.01.2015-15.11.2017 tarihleri arasında pnömoni nedeniyle hastanede yatan 180 hastanın retrospektif analizi yapıldı. TKP nedeniyle hastanede yatan 65 yaş üstü hastalar yatış gününden itibaren 30 güne kadar mortalite için takip edildi. Taburcu olanlar ise 90 güne kadar takip edildi. Hastane maliyeti analiz edildi.

Bulgular: 115 (%60) hasta 65 yaş üstüydü. Hastaların %82.4'üne oksijen tedavisi, %27.8'ine noninvaziv mekanik destek uygulandı. %16.5 hastada yoğun bakım desteğine gerek duyuldu. Pnömoni ciddiyet indeksi (PCİ) yaşla birlikte arttı (p=0.021). Otuz günlük mortalite oranı artmış yaşla ilişkiliydi (p=0.048). Toplam tedavi maliyetinin yüksek PCİ ile arttığı izlendi (p=0.003). Yüksek PCİ ve toplam maliyet özellikle mortalite ile ilişkiliydi (p=0.000). Otuz günlük mortalite oranı ileri yaşla ilişkili bulunurken (p=0.048) 60 ve 90 günlük mortalite oranlarında bu ilişki gösterilemedi (p=0.244, p==0.469). 30 günlük mortalite oranı kronik obstrüktif akciğer hastalığı (KOAH) ve malignitesi olanlarda yüksekti (p=0.038, p=0.040). Hastane maliyeti ve ek hastalıklar arasında bir ilişki bulunamadı (p>0.05).

Sonuç: TKP yaşlı hastalarda yaygın bir hastane yatış nedenidir. Yaşlı hastalarda TKP yüksek ölüm oranı ve artmış tedavi maliyeti nedeniyle daha önemlidir. Erken ve yeterli tedavi için risk faktörü olan yaşlı hastaların tespiti önemlidir.

Anahtar Kelimeler: Yaşlı, Hastane Yatışı, Toplum Kökenli Pnömoni, Maliyet

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Introduction

Community-acquired pneumonia (CAP) is one of the leading cause of death worldwide, and the most common infections leading to hospitalizations especially in people aged ≥ 65 (1,2) in developed countries. In Europe, the reported rate of CAP ranges from 1.6 - 9 cases per 1000 in adult population per year (3). According to data from United Nations World Prospects, population ageing worldwide is rapidly accelerating from 962 million people aged over 60 years in 2017 to an estimated 2 billion people by 2050 (1,4,5). Age, male sex, smoking, alcohol use, and many comorbidities such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, congestive heart failure, cancer, immunosupressive conditions, and Alzheimer's Disease are risk factors for CAP (6,7). Older people have a high prevalence of multiple comorbidities and older people have decreased efficiency of immune system that increases the infectious diseases (4).

The most common methods to classify the severity of CAP are the CURB - 65 and pneumonia severity index (PSI) systems. Higher PSI scores have increased the rate of hospitalization, length of hospital stay, rate of admission to the intensive care unit (ICU) and the mortality rate (6,8). Among the patients who are hospitalized for CAP, 10 - 20% are admitted to ICU. The mortality rate is high and overall 30-day mortality ranges up to 23%, 1-year mortality ranges up to 28%. Full recovery after hospitalization from CAP is generally slow and readmissions are frequent in patients aged ≥ 65 years, and this results in a significant clinical and economic burden for health systems.

In the US (United States), the cost of CAP is reported to be over $17 billion per year. The cost of treating CAP requiring hospitalization is high and increases with the level of severity of CAP (9,10). Each hospitalizations and readmissions increases the total cost in elderly patients.

In this study the characteristics and economic burden of hospitalized elderly patients (> 65 years) due to community-acquired pneumonia were analyzed.

Materials and Methods

Retrospective study included patients who were hospitalized with CAP between 01.01.2015 - 15.11.2017 were analyzed. Patients older than 65 years old and hospitalized for CAP were followed up for up to 90 days from initial hospitalization for mortality and these patients who were discharged alive within 30 days of initial hospitalization were followed up to 90 days of initial hospitalization for re-hospitalization.

CAP diagnosis was based on clinical criteria (cough, dyspnea, sputum expectoration, fever and / or chest pain) and radiological confirmation (pulmonary infiltration on chest x - ray). Sociodemographic variables such as age, gender, smoking status, comorbidities were collected. Severity of illness classified using PSI score consisted of 4 parts, demographics including age and sex, comorbidity, physical examination, and laboratory findings. PSI at admission, radiological findings, length of stay (LOS), oxygen usage, mechanical ventilation (MV) support (noninvasive / invasive), ICU admission, mortality, hospital costs, 30-day and 90-day mortality and readmissions were recorded. We contacted patients or their families by phone to identify survival and clinical information if the patients were not followed up regularly.

Statistical Analysis:

Statistical analyses were performed using SPSS 18.0 software (IBM Corporation). Descriptive and summary statistics (mean, standard deviation) were obtained for continuous variables. Frequencies were accessed for each level of categorical variables, qualitative variables were compared using the Pearson's chi - squared test, Kolmogorov Smirnov test was used for non-categorical variables. For correlations we used Spearman's rho correlation coefficient. All p -values were considered significant for $p < 0.05$.

Results

The study population consisted of 115 (60%) hospitalized patients who were > 65 years old with community - acquired pneumonia. 65 of 180 patients hospitalized with the diagnosis of CAP were not included in the study because they were younger than 65 years of age. There were 83 males (72.2%) and 32 females (27.8%), and the mean age was 75.8 ± 7.50. Ninety-seven patients (89.8%) had at least one additional disease. 56 (48.7%) patients COPD, 41 patients (35.7%) had cardiac problems, 20 (17.4%) patients had diabetes mellitus, and 21 (18.3%) patients had dementia or Alzheimer, and 12 patients (10.4%) had malignancy. 75.7% of the patients had a smoking history. Table 1 summarizes the baseline characteristics of the study population.

In 63% of the patient's pneumonia was unilobar and 20.4% of the patient's pneumonia was accompanied with pleural effusion. The mean length of hospital stay among older patients with CAP was 6.88 ± 4.64 days. Most (82.6%) of the patients needed oxygen therapy support because of hypoxic respiratory failure and 28.7% of them received noninvasive mechanical ventilation (NIMV) support during treatment period. 16.5% of the patients needed intensive care support and 73.6% of the patients who were admitted to the ICU were intubated and followed with invasive mechanical ventilation. PSI was 123.18 ± 37.9 (class 3 - 5). Total hospital cost was 323.6 ± 560.6 $.

PSI was increased with age, as expected. Total treatment costs were increased with high PSI (p = 0.003). Increased PSI and total cost were significantly associated with mortality (p = 0.000). 9.3% of the patients died in hospital during hospitalization. 30-day mortality was related with older age (p = 0.048), but age was not related with 60-day and 90-day mortality (p = 0.244, p = 0.469). 30-day mortality was high in patients with COPD and malignancy (p = 0.038, p = 0.040). No associations were found between total hospital cost and additional diseases (p > 0.05) (Table 2-3).

Table 1
Characteristics of Patients With Community-Acquired Pneumonia

Patient Characteristics	
Age (mean)	76.5±7.20
Gender (M/F) (%)	74.1 / 25.9
Comorbidity (%)	89.8
With a smoking history, (%)	76.9
Nursing home residents (%)	5.6
Hospital length of stay (mean)	6.88 ± 4.64
PSI (mean)	122.79 ± 37.3
Total hospital cost (mean) ($)	323.6 ±560.6
Hospital mortality (%)	9.3
30-day mortality (%)	13.9
60-day mortality (%)	6.1
90-day mortality (%)	5.2
Oxygen requirement (%)	82.6
NIMV requirement (%)	28.7
ICU requirement (%)	16.5
IMV requirement	12.2

Table 2
P Values Of The Correlations Between Comorbidity And Different Variables

	Age	**PSI**	**Cost**	**LOS**	**ICU**	**30-day mortality**	**60-day mortality**	**90-day mortality**
COPD	0.794	0.160	0.376	0.414	0.104	0.038*	0.224	0.365
DM	0.022*	0.585	0.944	0.313	0.129	0.892	0.829	0.958
Malignancy	0.005*	0.168	0.271	0.149	0.897	0.040*	0.517	0.548
Demantia	0.000*	0.103	0.069	0.957	0.344	0.156	0.420	0.297
CVD	0.012*	0.293	0.020*	0.052	0.099	0.252	0.404	0.440
Renal Disease	0.739	0.011*	0.184	0.771	0.195	0.359	0.503	0.535
Cardiac Disease	0.773	0.286	0.106	0.463	0.952	0.067	0.052	0.709

*Correletion is significant at the 0.05 level

Table 3
Evaluation Of The Relationship Between Mortality And Age, Cost And PSI Spearman Correlation Test

	30 day mortality	60 day mortality	90 day mortality
Age	**r=0.198**	r=0.115	r=0.068
	p=0.048	p=0.242	p=0.492
PSI	**r=0.331**	r=0.114	r=0.170
	p<0.001	p=0.247	p=0.086
Cost	r=0.058	r=0.060	r=0.013
	p=0.542	p=0.549	p=0.899

Discussion

This is a retrospective study to assess the influence of age, comorbidity, PSI scores on outcomes of hospitalized elderly patients with CAP in a pulmonology department of the hospital.

Community - acquired pneumonia are more frequently and with more severe consequences on elderly patients than younger populations. As the population ages, it is expected that the medical and economic

impact of this disease will increase. In Japan 1.9 million new CAP cases every year and approximately 70% of them are > 65 years old and 70% of these elderly patients are hospitalized. Age, male sex and comorbidities are risk factors for CAP (6).

Elderly people suffer from comorbidities that affect their immune system so the pneumonia increases. 89.8% of the patients in the study group had underlying comorbidities. In our patients it was mostly 48.7 % COPD, because our hospital is a chest training hospital, the second mostly seen was chronic heart diseases. Most of the studies have shown that underlying comorbidities increase the risk of hospitalizations. In Campling et al study most of the patients (33.7%) had chronic respiratory diseases like our study (11). In Han et al study, the mostly seen underlying conditions were cardiovascular disease (54.2%) and chronic respiratory diseases (31.7%) like our study (12). Risk factors for CAP include advanced age and underlying diseases especially chronic pulmonary diseases, also increase the hospitalizations and adverse outcomes in elderly CAP patients (4,9,11).

CAP should be prioritized for prevention in older adults with strategies such as vaccination and smoking cessation.

PSI and CURB - 65 are the most commonly used scores for decision in hospitalization and for predicting short - term mortality. Major limitation for PSI score in elderly patients is a heavy weight given to the age variable, so it can be high in older patients. However most of the studies show that higher PSI scores is associated with higher mortality, especially 30-day mortality. PSI was class 3-5 in our study. PSI was increased with age ($p = 0.021$). PSI was significantly associated with mortality ($p = 0.000$) (4,11,13,14,15).

CAP is associated with clinical and economical burdens in most of the countries. Especially in elderly patients hospital admissions are increasing and this increases the total hospital costs. Total hospital cost in our study was 323.6 ± 560.6 dollars. The total cost was low because most of the patients (83.5%) were followed and treated in the pulmonary clinic and the costs would be higher in intensive care units. In our study total treatment costs were increased with high PSI ($p = 0.003$). PSI increased in elderly patients, so the treatment costs were high in elderly because of different treatment modalities and they needed more support of intensive care unit. Many literatures studied the economic burden of CAP in elderly patients and found that the treatment costs increased with age and PSI similar to our study (6). The most important factor for the costs is hospitalizations. Economic burden can be reduced by decreasing the hospitalization of mild cases (6,16,17).

In this study 9.3% of the patients died in hospital during hospitaliszation. In Ma's and coworkers study, 12.3% patients died during hospitalization similar to our study (18). In Calle's study mortality was higher (24%) than other authors and they emphasized that all their cases over 75 years old and had poor health status (13). The studies have reported the mortality rates 6.4% to 33% because of the increased age, severity of the pneumonia and underlying comorbidities (12).

Our mortality rates were respectively 13.9%, 6.1% and 5.2% 30-day, 60-day and 90-day mortality. 30-day mortality was related with older age ($p = 0.048$), but age was not related with 60-day and 90-day mortality ($p = 0.244$, $p = 0.469$) in our study. In Han's et al study, in hospital mortality and 60-day mortality were significantly increased with age, as well (12). In our study 30-day mortality was slightly higher than other studies it could be because of age, high PSI values and comorbidities. Also we found that in patients with COPD and malignancy 30-day mortality were higher than other patients ($p = 0.038$, $p = 0.040$). Almost half of the CAP patients (48.7%) were with COPD, so 30-day mortality could be higher. Most of our patients had respiratory failure and required oxygen treatment (82.6%), 28.7% of the patients needed the support of noninvasive mechanical ventilation and 12.2% of them required invasive mechanical ventilation. In Han's study congestive heart failure was the only predictor with mortality (12). In Dai's et al study compared in hospital mortality and 60-day mortality of COPD - CAP and nonCOPD - CAP patients and found the mortalities higher in COPD - CAP patients but there were no significant difference between them [19]. Also neoplastic diseases were associated with short - term mortality (15).

Because of high morbidity and mortality of CAP especially in elderly group, vaccination is an important preventative therapy. In order to prevent CAP, the guidelines recommend smoking cessation, influenza vaccination, and pneumococcal vaccinations for adults aged ≥ 65 years. However substantial underuse of influenza and pneumococcal vaccination exists in this population. Although this point is controversial because some investigators also have concluded that the efficacy of vaccination may be reduced in elderly individuals (20). In our study ninety - six patients (83%) did not have any vaccination. Vaccination was not mostly recommended to our study group, so health workers should be alert to vaccinations as a preventative therapy especially in elderly patients.

Vaccination can be administered in routine outpatient settings or upon discharge in patients hospitalized for any condition. Thus smoking cessation measures are particularly important for preventing CAP in older individuals (21,22). Other tactics, such as oral care and prevention of aspiration, have been studied extensively in nursing home and hospitalized patients, but further research is needed to determine if these findings can be applied to patients at risk for CAP.

Prioritization of CAP prevention is needed to substantially reduce the burden of CAP.

Limitation:

Our limitation for this study was that it was a retrospective study and the population was so small. The number of our population is considered to be insufficient because of incomplete coding of pneumonia. Again for this reason, a comparison could not be made since the number of our cases under 65 years of age was low.

Conclusion

The population is getting older in nowadays and considering the morbidity, mortality and the economic cost associated with CAP in elderly patients (> 65 years) the preventive strategies should be applied. Strategies should be improving the evaluation, diagnosis, treatment and prevention of CAP in this aging population. Improvement of vaccination programme, anti - tobacco campaigns and correct oral hygiene are significant especially in the elderly population. Prioritization of CAP prevention is needed to substantially reduce the burden of CAP.

Ethics Committee Approval: Ethical permission was obtained from the scientific committee of Suat Seren Chest Diseases and Surgery Training and Research Hospital with the protocol number 49109414-806.02.02 dated 11.12.2017.

Informed Consent: Written consent was obtained from the participants.

Conflict of Interest: Authors declared no conflict of interest.

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References

1. Egger ME, Myers JA, Arnold FW, Pass LA, Ramirez JA, Brock GN. Cost effectiveness of adherence to IDSA/ATS guidelines in elderly patients hospitalized for Community-Aquired Pneumonia. BMC Med Inform Decis Mak 2016 Mar 15;16:34. doi: 10.1186/s12911-016-0270-y. PMID: 26976388.
2. Chen L, Zhou F, Li H, Xing X, Han X, Wang Y, et al. Disease characteristics and management of hospitalised adolescents and adults with community-acquired pneumonia in China: a retrospective multicentre survey. British Medical Journal Open 2018 Feb 15;8(2):e018709. doi: 10.1136/bmjopen-2017-018709. PMID: 29449294.

3. Almirall J, Bolíbar I, Vidal J, Sauca G, Coll P, Niklasson B, et al. Epidemiology of community-acquired pneumonia in adults: a population-based study. European Respiratory Journal 2000 Apr;15(4):757-63. doi: 10.1034/j.1399-3003.2000.15d21.x. PMID: 10780770.
4. Cilloniz C, Rodrigues-Hurtado D, Torres A. Characteristics and management of community-acquired pneumonia in the era of global aging. Medical Science 2018, 6(2):35. doi: 10.3390/medsci6020035. PMID: 29710871.
5. World Population Prospects: The 2017 Revision I Multimedia Library- United Nations Department of Economic and Social Affairs. Available online: https://www.un.org/development/desa7publications/world-population-prospects-the-2017-revision.html (accessed on 9 February 2018).
6. Konomura K, Nagai H, Akazawa M. Economic burden of community-acquired pneumonia among elderly patients: a Japanese perspective. Pneumonia (Nathan) 2017 Dec 5;9:19. doi: 10.1186/s41479-017-0042-1. PMID: 29226070.
7. Brown JD, Harnett J, Chambers R, Sato R. The relative burden of community-acquired pneumonia hospitalizations in older adults: a retrospective observational study in the United States. BioMed Central Geriatrics 2018 Apr 16;18(1):92. doi: 10.1186/s12877-018-0787-2. PMID: 29661135.
8. Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Şarkıcı DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. The New England Journal of Medicine 1997 Jan 23;336(4):243-50. doi: 10.1056/NEJM199701233360402. PMID: 8995086.
9. Sato R, Gomez Rey G, Nelson S, Pinsky B. Community-acquired pneumonia episode costs by age and risk in commercially insured US adults aged ≥50 years. Applied Health Economics and Health Policy 2013 Jun;11(3):251-8. doi: 10.1007/s40258-013-0026-0. PMID: 23605251.
10. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgraduate Medicine 2010 Mar;122(2):130-41. doi:: 10.3810/pgm.2010.03.2130. PMID: 20203464.
11. Campling J, Jones D, Chalmers JD, Jiang Q, Vyse A, Madhava H, et al. The impact of certain underlying comorbidities on the risk of developing hospitalised Pneumonia in England. Pneumonia (Nathan) 2019 Oct 11;11:4. doi: 10.1186/s41479-019-0063-z. PMID: 31632897.
12. Han X, Zhou F, Li H, Xing X, Chen L, Wang Y, et al. Effects of Age, Comorbidity and Adherence to Current Antimicrobial Guidelines on Mortality in Hospitalized Elderly Patients With Community-Acquired Pneumonia. BioMed Central Infectious Diseases 2018 Apr 24;18(1):192. doi: 10.1186/s12879-018-3098-5. PMID: 29699493.
13. Calle A, Marquez MA, Arellano M, Perez LM, Pi-Figueras M, Miralles R. Geriatric Assessment and Prognostic Factors of Mortality in Very Elderly Patients With Community-Acquired Pneumonia. Archivos de Bronconeumologia.2014;50(10):429-434. doi: 10.1016/j.arbres.2014.01.012. PMID: 24629763.
14. Kim MA, Park JS, Lee CW, Choi WII. Pneumonia Severity Index in Viral Community Acquired Pneumonia in Adults. Plos One 2019 Mar 6;14(3). doi: 10.1371/journal. pone.0210102. PMID: 30840626.
15. Viasus D, Cillóniz C, Cardozo CG, Puerta P, Garavito A, Torres A, et al. Early, short and long-term mortality in community-acquired pneumonia. Annals of Research Hospitals 2018;2:5 doi: 10.21037/arh.2018.04.02.
16. Huang SS, Johnson KM, Ray GT, Wroe P, Lieu TA, Moore MR, et al. Healthcare utilization and cost of pneumococcal disease in the United States. Vaccine 2011 Apr 18;29(18):3398-412. doi: 10.1016/j.vaccine.2011.02.088. PMID: 21397721.
17. Choudhury G, Chalmers JD, Mandal P, Akram AR, Murray MP, Kısa P, et al. Physician Judgement Is a Crucial Adjunct to Pneumonia Severity Scores in Low-Risk Patients. European Respiratory Journal 2011 Sep;38(3):643-8. doi: 10.1183/09031936.00172910. PMID: 21406507.
18. Ma HM, Tang WH, Woo J. Predictors of in-hospital mortality of older patients admitted for community-acquired pneumonia. Age and Ageing 2011 July;40(6):736-41. doi: 10.1093/ageing/afr087. PMID: 21771744.
19. Dai RX, Kong QH, Mao B, Xu W, Tao RJ, Wang XR, et al. The mortality risk factor of community acquired pneumonia patients with chronic obstructive pulmonary disease: A retrospective cohort study. BioMed Central Dec 2018;18(1). doi: 10.1186/s12890-018-0587-7. PMID: 29357862.

20. Stupka JE, Mortensen EM, Anzueto A, Restrepo MI. Community-acquired pneumonia in elderly patients. Aging health 2009; 5(6): 763–774. doi:10.2217/ahe.09.74. PMID: 20694055.
21. Hu G, Zhou Y, Wu Y, Yu Y, Liang W, Ran P. The Pneumonia Severity Index as a Predictor of In-Hospital Mortality in Acute Exacerbation of Chronic Obstructive Pulmonary Disease. PLoS ONE July 2015;10(7). doi:10.1371/journal. pone.0133160. PMID: 26186637.
22. Olasupo O, Xiao H, Brown JD. Relative Clinical and Cost Burden of Community-Acquired Pneumonia Hospitalizations in Older Adults in the United States—A Cross-Sectional Analysis. Vaccines (Basel) 2018 Sep; 6(3): 59. doi:10.3390/vaccines6030059. PMID: 30200286.