

Magnesium Level in the Mortality Prediction of Community-acquired Pneumonia Patients

Toplum Kökenli Pnömoni Hastalarının Mortalite Tahmininde Magnezyum Düzeyi

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Keywords

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Abstract

Objective: We aimed to examine the contribution of pneumonia severity index and blood magnesium (Mg) level of community-acquired pneumonia (CAP) patients who received inpatient treatment in our hospital to the mortality of the cases.

Materials and Methods: Our study is a retrospective study in which we applied to the emergency department (ED) of our hospital in 2018, with the diagnosis of CAP, and were hospitalized to the wards or intensive care unit (ICU).

Results: A total of 279 patients with CAP were enrolled in this study. All-cause mortality on the 28th day of follow-up was 13.6%. There were statistically significant results between the 2 groups (survivors and non-survivors), which were classified based on their 28-day mortality rates, in terms of the Mg, pneumonia severity index (PSI), and confusion, urea, respiratory rate, blood pressure, age >65 years (CURB-65) values. Moreover, the optimal Mg cut-off for predicting 28-day mortality at the time of ED admission was determined to be 1.90 mg/dL, with 71% sensitivity, 73% specificity, and 73% accuracy. ROC analysis revealed that the areas of Mg under the AUC in terms of 28-day mortality were 0.778. Thirty-eight patients died during the first 28-day period. Of these, 27 (64,2%) had Mg level <1.90 mg/dL. Independent predictors of 28-day mortality rates were determined to be Mg (lower than 1.90 mg/dL), CURB-65, PSI, vasopressor need and stay ICU.

Conclusion: Mortality rates increase as the Mg level decreases in CAP patients.

Öz

Amaç: Bu çalışmada hastanemizde yatarak tedavi gören toplum kökenli pnömoni (TKP) hastalarının pnömoni şiddet skorları ve kan magnezyum (Mg) düzeyinin olguların mortalitesine etkisinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamız, 2018 yılında hastanemizin acil servisinde TKP tanısı konulan ve servislere veya yoğun bakım ünitesine (YBÜ) yatırdığımız hastaları içeren retrospektif bir çalışmadır.

Bulgular: Çalışmaya toplam 279 TKP hastası alındı. Takibin 28. gününde tüm nedenlere bağlı mortalite oranı %13,6 idi. Hastaları 28 günlük mortalite durumlarına göre yaşayanlar ve yaşamayanlar olarak iki gruba ayırdığımızda, gruplar arasında Mg düzeyi, pnömoni şiddet indeksi (PSİ) ve konfüzyon, üre, solunum sayısı, kan basıncı, <65 yaş (CURB-65) değeri arasında istatistiksel olarak anlamlı bir fark vardı. Ayrıca acil servise ilk başvuru anında alınan kan tetkikinde çalışılan Mg değeri için cut-off değerini 1,90mg/dL olarak aldığımızda 28 günlük mortalite tahmini için sensitivitesinin %71, spesifitesinin %73, doğruluk oranının %73 olduğu görüldü. Mg ve 28 günlük mortalite için çalışılan ROC analizinde eğri altında kalan alanın 0,778 olduğu tespit edildi. Yirmi sekiz günlük takip boyunca 28 hastanın öldüğü görüldü ve bu hastaların 27'sinin (%64,2) Mg düzeyi 1,90 mg/dL altındaydı. 28 günlük mortalite oranları için bağımsız prediktörlerin belirlenmesi amacıyla yapılan lojistik analizde Mg (1,90 mg/dL'den düşük), CURB-65, PSİ, vazopresör ihtiyacı ve YBÜ'de kalışın bağımsız prediktörler olduğu belirlendi.

Sonuç: TKP hastalarında Mg seviyesi düştükçe ölüm oranları artmaktadır.

Introduction

Community-acquired pneumonia (CAP) continues to be a serious public health problem in Turkey, as in the rest of the world. According to The National Statistics Institute of Turkey data, it ranks 5th in terms of death rates due to lower respiratory tract infections (1). Today, antibiotic usage has become widespread, but mortality from pneumonia and morbidity have not decreased. It is usually accepted that the mortality rate of patients diagnosed with CAP is between 10-20% (2). For this reason, many markers and severity scores have been developed to help determine the clinical severity of cases in CAP patients (3). Our intention to use these severity scores and markers is to determine serious clinical status of the cases while the patient is in the emergency department (ED) and to start appropriate treatment early. For this purpose, most frequently used severity scores as confusion, urea, respiratory rate, blood pressure, age >65 years (CURB-65) and pneumonia severity index (PSI) have been used for a long time.

Magnesium (Mg) is one of the important cations in our body. It has a role in energy metabolism, intracellular calcium regulation, RNA and protein synthesis and degradation, cellular metabolic reactions such as energy production and storage as well as a role in the realization of physiological functions of major organs such as brain and heart (4,5). There are many publications in the literature discussing the relationship between Mg levels and hospital mortality. Mg level has been associated with clinical signs such as Mg deficiency, arrhythmias, heart failure, sudden death, muscle weakness, and seizures (5,6).

In this study, we started with the question of whether Mg levels can be used as a mortality determiner in CAP patients and we aimed to examine the relationship between PSI of CAP patients who received inpatient treatment in our hospital with Mg levels and the mortality of cases.

Materials and Methods

Study Design and Setting

This single-center, cohort study was conducted at Muğla Sıtkı Koçman University Training and Research Hospital. Our hospital has 510 beds. A daily average of 500 patients are admitted to our ED. Before

conducting the study, approval was obtained from the Muğla Sıtkı Koçman University Human Research Ethics Committee (decision number: 175, date: 09.08.2020). This is a retrospective study in which we investigated the clinical and laboratory findings of patients admitted to our hospital ED between January 1 and December 31, 2018.

Definitions and Clinical Scoring Tools

CAP was defined as the presence of new pulmonary infiltrations on lung imaging with fever, cough, sputum and/or pleuritic chest pain, none of which were acquired at a hospital. Hospital-acquired pneumonia (HAP) was defined as pneumonia occurring 48 hours after admission. Healthcare-associated pneumonia (HCAP) was defined for patients who [1] had undergone hospitalization (for ≥ 2 days), home infusion therapy, and/or home wound care in the preceding 90 days; [2] had undergone chronic dialysis within the last 30 days; [3] were residents of nursing home so extended care facilities; and/or (4) had family members with multidrug-resistant pathogens (7).

The severity of CAP was evaluated using the following parameters: confusion, urea [≥ 7 mmol/L (19 mg/dL)], respiratory rate (≥ 30 breaths/min), blood pressure (systolic blood pressure ≤ 90 mm Hg and/or diastolic blood pressure ≤ 60 mm Hg), age older than 65 years (CURB-65) (years) (13), and PSI scores (7).

Selection of Participants

We also examined the data of the patients who were hospitalized in the chest diseases ward or the intensive care unit (ICU) with the diagnosis of CAP. A list of the patients diagnosed and examined with the pneumonia codes J10, J12, J15, J17, and J18 from the hospital's Department of Information Technologies was taken and both their files and their imaging were examined retrospectively.

The inclusion criteria were as follows: over 18 years old, diagnosed with CAP, and hospitalized. The exclusion criteria included those younger than 18 years; pregnant; diagnosed with HAP, HCAP, or aspiration pneumonia; with known human immunodeficiency virus positivity; with a history of hematological disorders or immunosuppression (usage of immunosuppressive drugs within 90 days, solid organ transplantation, those who used prednisolone at doses of more than 10 mg/day in more than 14 days); diagnosed with active pulmonary

tuberculosis; with rheumatic disease; and who had undergone a recent blood transfusion.

Study Protocol and Follow-up Evaluation

In our hospital, as a general practice, these patients are evaluated by an emergency medicine specialist after being admitted to the ED. Complete blood count; glucose, kidney, and liver function tests; and electrolytes and CRP examinations are requested, a chest radiograph is taken, CURB-65 and PSI are calculated and pulmonologist consultation is requested.

The patients evaluated by a pulmonologist are hospitalized based on laboratory tests, in addition to prediction scores and social indications (living alone, patients with care problems, or patients with comorbidity). Hospitalizations are planned as ward or ICU by the pulmonologist who evaluated the patient, and the parameters used for hospitalization are also used for ward or ICU hospitalization indication.

All these data are saved in the patients' files and hospital automation system. In this context, the data of the patients were accessed from the automation system of our hospital and the individual patient files kept for the patients.

Data Collection

A form was created to be filled for each patient individually. The form included the following parameters: patient's age, gender, laboratory values (Mg level) obtained from the blood samples taken in the ED, CURB-65 and PSI scores calculated in the ED are also calculated and recorded.

Patients were followed up 28 days after the diagnosis of pneumonia. The following details were recorded during hospitalization: where the patient was hospitalized (ICU or ward), whether intubation was applied, vasopressors need, length of stay (LOS) in the hospital, intensive care hospitalization, and all-cause 28-day mortality rate.

The mortality of the patients discharged, whether there was readmission in the hospital system, and the phone number given during the registration to the hospital system were determined by telephone. Those who lived for 28 days were grouped as "survivors" and those who died within 28 days were grouped as "non-survivors."

Laboratory Methods

The blood test results of the patients at their first admissions to the ED of our hospital were reviewed.

During the study period, blood samples were drawn into tubes containing sodium citrate and analyzed under room temperature using Pentra DF Nexus, Hariba Medical device in the biochemistry laboratory. These blood samples were analyzed regarding Mg level (1.5-2.5 mg/dL).

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences 20.0 for Windows (SPSS Inc., Chicago, IL). Frequency analysis was used for descriptive analysis. A normal distribution of the quantitative data was checked using the Kolmogorov-Smirnov test. Parametric tests (Independent 0 samples t-test and posthoc Tukey test) were applied to the data of normal distribution (survivors/non-survivors = age and Mg), and non-parametric tests (Mann-Whitney U test and Kruskal-Wallis test) were applied to the data of questionable normal distribution (survivors/non-survivors = gender, LOS, hospitalization in ICU, vasopressors need, intubation in emergency service, CURB65, PSI, Mg). Continuous data were presented as mean \pm standard deviation or median (minimum-maximum), as appropriate. All differences associated with a chance probability of 0.05 were considered statistically significant. The area under the ROC curve was calculated to determine the diagnostic accuracy. The survival rate was calculated using the Kaplan-Meier method. Cyclooxygenase regression analysis was performed to determine variables associated with 28-day mortality. Sensitivity and specificity were determined to PSI and Mg for mortality. Sensitivity and specificity for mortality were determined to PSI and Mg.

Results

In our study, a total of 382 patients presenting to the ED with a diagnosis of pneumonia were enrolled. Of these, 9 were excluded due to HCAP, 8 were excluded due to HAP, 3 were excluded because they were pregnant, 10 were excluded because they were immunocompromised, and 7 were excluded because they had rheumatic diseases. After excluding these patients, the complete 28-day follow-up status was available for 345 patients with a diagnosis of CAP. Of these 345 patients, 66 patients admitted to the emergency service were excluded from the study by determining that their Mg levels were not studied, remaining 279 patients were included in the

study. It was observed that 196 (70.3%) of our cases were male and the average age was 69 ± 14 . It was determined that 22 (7.9%) cases required intubation in the ED, 39 (14%) patients were hospitalized to ICU from the ED, 29 (10.4%) patients needed vasopressors treatment, 30 (10.8%) patients died in the hospital. Eight (2.8%) patients died within 28 days after discharge. Demographic properties of our cases and Mg levels, CURB-65, PSI values are given in Table 1.

Patients were divided and compared into 2 groups as the survivors and the non-survivors according to their condition after 28-day and then compared, among the groups, it was observed that there was significant difference statistically in terms of gender ($p=0.011$), intubation in the ED ($p=0.000$), period in ICU stay ($p=0.000$), whether vasopressors need or not ($p=0.000$), hospitalized in ICU ($p=0.000$), Mg levels ($p=0.000$), CURB 65 ($p=0.000$), PSI ($p=0.000$), but there was no significant difference in terms of LOS ($p=0.674$) and age ($p=0.187$) (Table 2). In the mean analysis made to examine what meant these statistical differences, it was observed that male gender, LOS and stay in ICU, intubation in ED, vasopressor need, increasing of CURB 65 and PSI scores and but decreasing of Mg levels were associated with mortality (Table 1).

When the patients were divided and compared in 2 groups as "ICU inpatients" and "ward inpatients,"

we found statistically significant difference between the groups with age ($p=0.023$), gender $p=0.042$), intubation in the ED ($p=0.000$), vasopressor need ($p=0.000$), LOS ($p=0.023$), mortality ($p=0.000$), Mg levels ($p=0.000$), CURB-65 ($p=0.000$) and PSI ($p=0.000$) score (Table 2). In the mean analysis for interpreting what meant these statistical differences, we observed that ICU need increased by as the Mg levels and age decreased and increasing vasopressor need, increasing in the LOS, intubation in the ED, increasing the CURB-65 and PSI score (Table 2).

In our study, when we grouped Mg levels as 1,5 mg/dL and below (hypomagnesemia), 1.5-2.5 mg/dL (normomagnesaemia) 2.5 mg/dL (hypermagnesemia) and above, there are statistically significant changes between the groups in terms of 28-day mortality (Table 1) and hospitalization to ICU (Table 2). When these changes were examined, it was seen that as the Mg levels of the patients decreased, both their mortality and the rate of hospitalization to ICU increased.

In the ROC curve analysis, when the 28-day mortality with Mg level was applied, it was understood that the closer the area under the curve (AUC) was to 1, the more valuable the marker was. In the ROC curve analysis of the data we obtained in our study, it has been found that the area of Mg level was 0.778 under the AUC in terms of 28-day mortality

Table 1. The statistical results of the groups according to 28-day mortality (survivors-non-survivors)

| | Survivors n= 241 (86.4%) | Non-survivors n=38 (13.6%) | Total n=279 (100%) | p |
|---|-----------------------------|-------------------------------|-----------------------|-------|
| Age (years old \pm SD) | 68 \pm 14 | 72 \pm 10 | 69 \pm 14 | 0.187 |
| Gender (F/M) | 71/176 | 18/20 | 89/196 | 0.000 |
| Hospitalization in ICU (day) (min-max) | 1.07 (0-41) | 5.5 (0-21) | 1.6 (0-41) | 0.000 |
| Vasopressors need [cases (%)] | 11 (4.5) | 18 (47.3) | 29 (10.3) | 0.000 |
| LOS (day) (min-max) | 9 (2-28) | 12 (1-28) | 9 (1-28) | 0.674 |
| Intubation in emergency service [cases (%)] | 8 (3.3) | 14 (36.8) | 22 (7.8) | 0.000 |
| The place to stay (ICU/Ward) | 11/230 | 28/10 | 39/240 | 0.000 |
| CURB-65: (0-1 point:/2 point:/3-5 point) | 117/62/62 | 2/7/29 | 119/69/91 | 0.000 |
| PSI (70 point \leq :/70-130 point:/130 point \geq) | 25/138/76 | 0/12/28 | 25/150/104 | 0.000 |
| Mg (mg/dL) | 2.25 \pm 0.5 | 1.74 \pm 0.5 | 2.18 \pm 0.5 | 0.000 |
| Hypomagnesemia (under 1.5 mg/dL) | 5 | 17 | 22 | 0.000 |
| Normomagnesemia (1.5-2.5 mg/dL) | 167 | 15 | 182 | |
| Hypermagnesemia (above 2.5 mg/dL) | 69 | 6 | 75 | |

SD: Standard deviations, F: Female, M: Male, Min: Minimum, Max: Maximum, ICU: Intensive care unit, LOS: length of stay, CURB-65: Confusion, urea, respiratory rate, blood pressure, age >65 years, PSI: Pneumonia severity index, Mg: Magnesium level

Table 2. The statistical results of the groups “ICU inpatients” and “ward inpatients”

| | Ward inpatients n=240 (68%) | ICU inpatients n=39 (14%) | Total n=279 (100%) | p |
|---|--------------------------------|------------------------------|-----------------------|-------|
| Age | 69±14 | 65±11 | 69±14 | 0.023 |
| Gender (F/M) | 72/174 | 17/22 | 89/196 | 0.042 |
| Vasopressors need [cases (%)] | 6 (2.5) | 23 (79.3) | 29 (10.3) | 0.000 |
| LOS (day) (min-max) | 9 (1-28) | 12 (1-28) | 9 (1-28) | 0.023 |
| Intubation in emergency service [cases (%)] | 0 (0) | 22 (56.4) | 22 (7.8) | 0.000 |
| In-hospital mortality (survivors/non-survivors) | 240/6 | 39/24 | 279/30 | 0.000 |
| CURB-65: (0-1 point:/2 point:/3-5 point) | 119/66/55 | 0/3/36 | 119/69/91 | 0.000 |
| PSI (70 point ≤:/70-130 point:/130 point ≥) | 25/140/75 | 0/10/29 | 25/150/104 | 0.000 |
| Mg (mg/dL) | 2.27±0.5 | 1.59±0.3 | 2.18±0.5 | 0.000 |
| Hypomagnesemia (under 1.5 mg/dL) | 6 | 16 | 22 | 0.000 |
| Normomagnesemia (1.5-2.5 mg/dL) | 151 | 31 | 182 | |
| Hypermagnesemia (above 2.5 mg/dL) | 74 | 1 | 75 | |

F: Female, M: Male, ICU: Intensive care unit, LOS: Length of stay, CURB-65: Confusion, urea, respiratory rate, blood pressure, age >65 years, PSI: Pneumonia severity index, Mg: Magnesium level

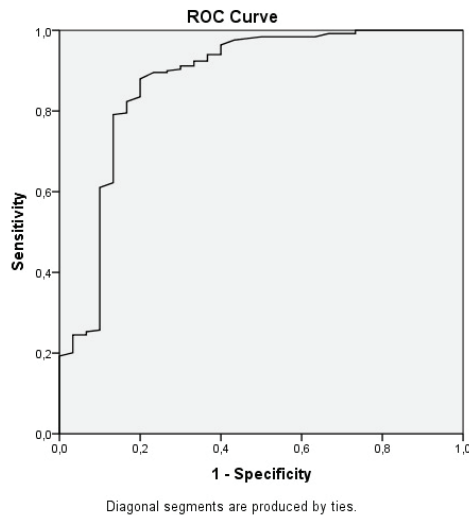


Figure 1. ROC analysis showing the relationship of Mg level with mortality

ROC: Receiver operating characteristic, Mg: Magnesium

(Figure 1). Based on Mg level of 1.90, it was seen that the sensitivity for 28-day mortality was 71.0% and the specificity was 73.4%. Based on PSI value of 70 points and above, it was seen that the sensitivity for intra-hospital mortality was 68.4% and the specificity was 67.6%. When the average value of CURB-65 severity score of 2 points and above was taken as cut-off value, the rates of sensitivity and specificity for intra-hospital mortality were calculated respectively as 94.7% and 48.5% (Table 3).

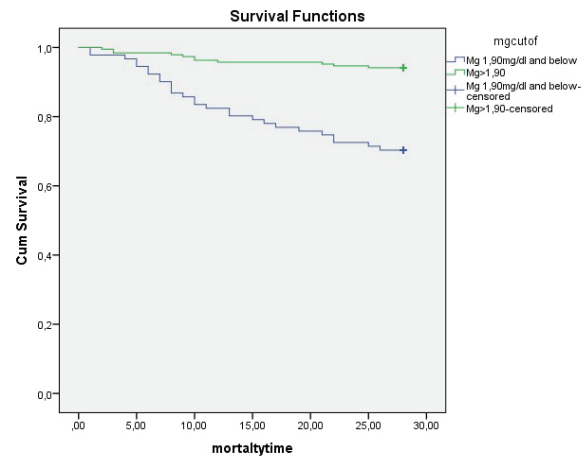


Figure 2. Kaplan-Meier survival curve according to Mg level above and below optimal cut-off value (1.90) for 28-days mortality

Mg: Magnesium

Thirty-eight patients died during the first 28-day period. Of these, 27 (71.0%) had Mg level <1.90 mg/dL (p<0.001). Figure 2 shows the Kaplan-Meier survival curve for Mg level according to these cutoff values. Patients with Mg levels below the cutoff value had significantly higher mortality rates than those with Mg level above the cutoff at 28-days (p<0.001), (Figure 2). Independent predictors for 28-day mortality rates were determined to be Mg level (lower than 1.90 mg/dL), CURB-65, PSI, vasopressor need and stay ICU (p<0.001, Table 4)

Table 3. Sensitivity and specificity in terms of 28-day mortality according to Mg \leq 1.90 mg/dL, PSI \geq 70 score, CURB-65 \geq 2 score

| Mg \leq 1.90 mg/dL | Mortality Yes | Mortality No | Sensitivity | Specificity | Accuracy | PPV | NPV |
|----------------------|---------------|--------------|-------------|-------------|----------|-------|-------|
| Positive | 27 | 64 | 71.0% | 73.4% | 73.1% | 29.6% | 94.1% |
| Negative | 11 | 177 | | | | | |
| PSI \geq 70 point | Mortality Yes | Mortality No | Sensitivity | Specificity | Accuracy | PPV | NPV |
| Positive | 26 | 78 | 68.4% | 67.6% | 67.7% | 25.0% | 93.1% |
| Negative | 12 | 163 | | | | | |
| CURB 65 \geq 2 | Mortality Yes | Mortality No | Sensitivity | Specificity | Accuracy | PPV | NPV |
| Positive | 36 | 124 | 94.7% | 48.5% | 54.8% | 23.5% | 98.3% |
| Negative | 2 | 117 | | | | | |

CURB-65: Confusion, urea, respiratory rate, blood pressure, age >65 years, PSI: Pneumonia severity index, Mg: Magnesium level, PPV: Positive predictive value, NPV: Negative predictive value

Table 4. Cox regression analysis analysis for the prediction of 28-day mortality

| Variables for 28 d | Odds ratio | 95% CI | p |
|--------------------|------------|--------------|-------|
| Mg | 5.762 | 2.857-11.623 | 0.000 |
| CURB-65 | 4.282 | 2.477-7.405 | 0.000 |
| PSI | 3.722 | 1.953-7.094 | 0.000 |
| Stay ICU | 1.067 | 1.030-1.097 | 0.011 |
| Vasopressor need | 11.154 | 5.869-21.199 | 0.000 |

Age: >65 years, COX: Cyclooxygenase, Confidence interval: CI, Mg: Magnesium level, CURB-65: Confusion, urea, respiratory rate, blood pressure, age >65 years, PSI: Pneumonia severity index, ICU: Intensive care unit

Discussion

In our study, we determined that Mg level was a valuable parameter in determining the 28-day mortality and hospitalization to ICU for CAP patients.

In the studies investigating the relationship between Mg level and mortality, it is stated that both decreasing and increasing of Mg levels are associated with mortality. Since Mg plays a role in cellular metabolism, energy metabolism, ion transfer of calcium and potassium, it seems likely to cause death due to cardiac events (5,6). Thongprayoon et al. (8), in their study examining the relationship between Mg level and hospital mortality, state that both hypomagnesemia and hypermagnesemia are associated with mortality. They also claim that as the increasing and decreasing rate of Mg level has increased, mortality has increased within itself.

In another study, it was stated that hypomagnesemia caused mortality by preparing for cardiac arrhythmia (4,9). In their studies on the same

subject, Cheungpasitpoan and colleagues stated that hypermagnesemia has been more effective than hypomagnesemia in terms of its effect on the mortality for 1 year of their patients (5). In another study in which the mortality of patients hospitalized in the ICU is studied, it was stated that hypomagnesemia was associated with mortality (6,10). In our study, we have observed that our cases had normomagnesaemia, but mortality increased as the mg level approached the lower limit of normal. Although it is close to the lower limit, we think that the increase in the mortality with the decrease of Mg level does not contradict the current literature.

So how is the relationship between respiratory diseases and Mg levels? Due to the relaxation and immunomodulating effect of Mg levels to the respiratory system, it is still used in respiratory diseases such as asthma, although it is not as common as before. Maybe for this reason, we can see hypermagnesemia more frequently in respiratory diseases (4). There are already studies indicating that hypermagnesemia are common to both the increase in the rate of hospitalization to ICU and in the mortality of respiratory diseases (4,11). There are also studies arguing that hypermagnesemia is related with longer stay in ICU and vasopressor need for a longer period of time (11,12). In our study, the situation is different from the above mentioned cases. The average of Mg level for our patients with lower respiratory tract infections is within the normal range and hypermagnesemia is not related with more mortality than hypomagnesemia. In addition, it seems to be also more related with hospitalization

to ICU and hypomagnesaemia. We cannot clearly state what reason is for this. Although the relation of hypomagnesemia and mortality is a new finding in terms of CAP, we think that it would not be correct to say that our data contradicts the literature because hypomagnesemia is related with mortality in the general population.

Many markers are used to estimate the mortality of CAP patients. CURB 65 and PSI are two of them and are also used in our hospital (3). Madhu et al. (3) in their study, stated that PSI and CURB-65 are related with mortality and mortality increases with increasing scores. Marti et al. (13) stated that PSI and CURB-65 were successful in predicting hospitalization to ICU patients in their metaanalysis. In our study, in accordance with the literature, these scoring results are directly proportional to mortality and hospitalization to the ICU. Thus, as the score points increase, the severity and mortality of pneumonia increases. In our study, Mg level was used as an additional mortality marker. It was observed that Mg level is close to both PSI and CURB-65 in terms of mortality estimation.

Study Limitations

There are some limitations in our study. Firstly, our study is a retrospective study and it is difficult to generalize as it concerns only one city. Secondly, during the study, the files of the patients were examined and it could not be reached to all data related to Mg level. Thirdly, other factors need to be excluded to think that patient mortality is only related to Mg level, but for this, a prospective study planning is needed.

Conclusion

As a result, mortality rates increase as the Mg level decreases of CAP patients. As the Mg level decreases, the 28-day mortality increases and the need for hospitalization to ICU also increases.

Ethics

Ethics Committee Approval: Before conducting the study, approval was obtained from the Muğla Sıtkı Koçman University Human Research Ethics Committee (decision number: 175, date: 09.08.2020).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.A., H.G., A.D., B.Y., Concept: E.A., H.G., Design: E.A., H.G., Data

Collection or Processing: H.G., A.D., B.Y., Analysis or Interpretation: E.A., Literature Search: E.A., B.Y., Writing: E.A., A.D.

Conflict of Interest: No conflict of interest was declared by the authors.

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