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**Whatsapp:** +90 505 865 63 06 (Only Message)

**Telephone**: +90 312 511 96 40

**E-mail:** editor@jeimp.com

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Original Article

# Retrospective Analysis of Prognostic Factors in Patients with Small Cell Lung Cancer

[1]Şimal Köksal Cevher [2]Nuriye Yıldırım Özdemir [3]Erdal Eskioğlu
1.Health Sciences University, Ankara Bilkent City Hospital, Department of Nephrology, Ankara, Turkey
2.Gazi University, Faculty of Medicine, Department of Internal Diseases and Oncology, Ankara, Turkey
3.Health Sciences University, Numune Training and Research Hospital, Department of Internal Medicine, Ankara, Turkey

**Corresponding author:** Şimal Köksal Cevher, MD. Ankara Bilkent City Hospital, Department of Nephrology, Universiteler Mah. Bilkent, Ankara, Turkey
E-mail: simkoksal@hotmail.com
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## ABSTRACT

**Background:** The goal of this study is to examine how small cell lung cancer (SCLC) prognosis and survival are impacted by pre-treatment clinical characteristics and laboratory data.

**Material and Method:** The 118 patients diagnosed with SCLC in our center between August 2000 and December 2008 were evaluated retrospectively. The effects of the 19 variables [hemoglobin (Hgb), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), albumin, sedimentation, sodium (Na), neuron-specific enolase (NSE), carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA 15-3), cancer antigen 125 (CA 125), cancer antigen 19-9 (CA 19-9), alpha-fetoprotein (AFP), performance status (PS), stage, sex, weight loss, age, smoking, chemotherapy (CT) related to the prognosis on survival were thoroughly investigated in detail. Statistically, univariate analyses were performed via Kaplan-Meier Method and multivariate analyses were performed via the Cox proportional hazards (Cox PH) model. The covariates that were found to have a significant relation ($p<0.05$) on prognosis in univariate analyses and the ones with $p<0.15$ in the univariate analyses were subjected to multivariate analysis to determine independent prognostic factors.

**Results:** In univariate analyses, albumin, Na, NSE, CA 125, stage, and sex had a significant relation to prognosis ($p<0.05$). In multivariate analyses, only the stage parameter was found to be an independent predictive factor on prognosis ($p=0.019$).

**Conclusion:** The knowledge of prognostic factors like the laboratory and clinical parameters and staging of the patients were considered to have a directing role in determining treatment strategies and clinical follow-up in SCLC.

**Keywords:** Small cell lung cancer, prognostic factors, survival, lung cancer

## INTRODUCTION

The leading cause of cancer-related death worldwide is lung cancer (1). Small cell lung cancer (SCLC) is regarded as a distinct entity from non-small cell lung cancer (NSCLC) due to its being observed mostly in smokers, its rapid growth, and the development of early metastases. SCLC, which constitutes 15-25% of lung cancer cases, is characterized by rapid dissemination, early metastasis, low survival rate, and short mean survival (2). At the time of diagnosis, approximately two-thirds of patients with SCLC are in the extensive stage, and one-third are in the limited stage (3). Compared to other lung cancers, SCLC has a worse prognosis and lower survival rates.

Typically, SCLC patients do not consult a physician until their symptoms worsen and become evident. At the time of diagnosis, most SCLC patients are in the extensive stage. Staging determines prognosis and treatment. The operation plays a minor role in the treatment of the disease. Less than 10% of patients with the lung-confined disease are candidates for thoracotomy. In staging, the Veterans' Administration Lung Study Group (VALSG) uses a simpler two-stage system instead of the tumor-node-metastasis (TNM) staging system that is used in most types of cancer (4). In the VALSG system, the limited stage is defined as the disease being limited to

a hemithorax containing the "tolerable" radiation area. All other patients are considered to be at the extensive stage of the disease. The distinction between the limited and the extensive stage is important since patients with limited stages can benefit from the combined treatment regimen.

Knowing a number of prognostic factors at the time of diagnosis is important in predicting the clinical outcome in cancers such as SCLC, which have an aggressive course and have a very low long-term survival rate. In addition, knowing some predictive factors that will determine the treatment toxicity and the response to treatment is crucial for patient selection and estimating treatment response.

## MATERIALS AND METHODS

*Study Design and Data Source*

In our retrospective observational analytical study, the 118 patients diagnosed with SCLC in the Medical Oncology Clinic of our center between August 2000 and December 2008 were analyzed retrospectively in order to investigate whether pre-treatment clinical features and laboratory parameters have an effect on prognosis and survival. The data of the variables being examined was obtained from the medical records. The follow-up period started on 01.08.2000, the first diagnostic data of the 118 patients; It terminated on 16.11.2009, covering the date of the last exitus case noted in this group (15.11.2009). A statistical study was performed on the 19 covariates that were deemed to be related to prognosis. The 6 covariates that were found to have a significant relation ($p<0.05$) on prognosis plus the 4 covariates with $p<0.15$ in univariate analyses were taken to multivariate analysis in order to determine independent prognostic factors. The variables deemed to be related to prognosis and survival are shown in **Table 1**.

## STATISTICAL ANALYSIS

The Predictive Analytics Software Statistics 18 (PASW Statistics 18) package program was used to conduct the statistical analysis. To compare the groups as pairs, we employed the Mann-Whitney U test.

For survival analysis, univariate statistical analyses were performed using the Kaplan-Meier method; logrank (Mantel-Cox), Breslow (Generalized Wilcoxon), and Tarone-Ware tests were used to examine the effects of a total of 19 covariates on prognosis.The variables that were found to have an eligible relation on survival (i.e., significance with $p<0.15$) by the Kaplan-Meier method in univariate statistical analyses were added to the multivariate model as candidate risk factors. Multivariate regression analyses were realized via the Cox PH model. The 95% confidence intervals of the variables were calculated. All tests were performed with a 95% confidence interval. All results with $p<0.05$ were considered statistically significant.

**Table 1.** Prognostic factors for survival

| Category of variable | # | Covariates |
|---|---|---|
| Hemogram | 1 | Hgb |
| Biochemistry | 2 | LDH |
| | 3 | ALP |
| | 4 | Albumin |
| | 5 | Na |
| Sedimentation | 6 | Sedimentation |
| Tumor Markers | 7 | NSE |
| | 8 | CEA |
| | 9 | CA 15-3 |
| | 10 | CA 125 |
| | 11 | CA 19-9 |
| | 12 | AFP |
| Other | 13 | Performance status |
| | 14 | Stage |
| | 15 | Sex |
| | 16 | Weight loss |
| | 17 | Age |
| | 18 | Smoking |
| | 19 | CT |

Hgb; hemoglobin, LDH; lactate dehidrogenase, ALP; alkaline phosphatase, Na; sodium, NSE; neuron-specific enolase, CEA; carcinoembryonic antigen, CA; cancer antigen, AFP; alpha-fetoprotein, CT; chemotherapy

## RESULTS

The mean age of 118 patients was 55.98±11.83 years (min:29.97, max:82.00). Out of 118 patients, 38 (84%) of 45 elderly patients (≥60 years old) and 54 (74%) of 73 patients (<60 years old) were found to be exitus in the follow-up period. The mean survival of elderly patients was 15.17±2.77 months, and the mean survival of other patients was 19.84±2.01 months (mean survival of 118 patients: 18.80±1.90 months). No significant effect of the age variable on survival was observed ($p=0.053$); however, the Breslow and Tarone-Ware tests gave statistically significant results ($p=0.040$ and 0.037). Of the 118 patients, 106 (89.8%) were male and 12 (10.2%) were female. The mean survival time was 16.92±1.84 months in male patients and 33.86±5.34 months in female patients, and the sex covariate was found to be significant on survival ($p=0.004$).

Among 118 patients, 19 (68%) of 28 with weight loss died, and 73 (81%) of 90 without weight loss died. The mean survival of those with weight loss was 23.19±5.13 months, and those without weight loss were 17.06±1.57 months. There was no significant effect of weight loss on survival ($p=0.645$).

Smoking history data of 116 (98.3%) of 118 patients were obtained. Those who had been exposed to cigarettes (current smokers and those who have quit) and those who had not been exposed (never smoked)

were analyzed in the variable "smoking exposure". When the survival data were handled separately with the variables "smoking exposure" and "smoking (during diagnosis)" as the only variable via the Kaplan-Meier model, no significant difference was found according to the logrank (Mantel-Cox) test (p=0.674 and 0.333, respectively). Mean survival time was observed to be 18.24±2.06 months in smokers (95% confidence interval: 14.15–22.20 months), and 20.75±3.84 months in non-smokers (95% confidence interval: 13.18–28.19 months).

Staging data were available for 114 of the 118 patients; 79 (66.9%) were in the extensive stage and 35 (29.7%) were in the limited stage. The mean survival time was found to be 26.91±4.39 months in limited-stage patients and 14.81±1.60 months in extensive stage patients. This difference was statistically significant (p=0.016). The disease being in the extensive stage was found to be a bad prognostic factor. The stage was found to be an independent prognostic factor in both uni-covariate Kaplan-Meier model analyses and multi-covariate Cox PH model analyses (p=0.016 and p=0.019, respectively). Differences in laboratory findings between stages were also evaluated, and a significant difference was observed between stages in ALP and CEA parameters (p=0.011, p=0.016, respectively). The values determined in the stage comparisons and p values are shown in **Table 2**.

As for chemotherapy (CT), the patients were divided into two groups: those treated with Etoposide-Cisplatin (EP) and those treated with other chemotherapeutic agents. Of 118 patients, 102 (86.4%) received CT, and 16 did not. Of the patients who received CT, 69 (77%) of 90 (88.24%) were treated with EP, and 9 (75%) of 12 (11.76%) were treated with other chemotherapeutic agents died. Mean survival in patients treated with EP and other agents was 19.76±2.10 months and 11.47±3.83 months, respectively. In CT, there was no significant difference between EP and treatment with other agents (p=0.129). When the patients who received CT and those who did not receive CT were compared, the following data were obtained: Mean survival in patients who did not receive CT was 13.88±3.76 months, and in patients who received CT, it was 18.99±1.99 months; no significant difference was found between receiving and not receiving CT (p=0.407).

Performance status (PS) was determined by the Eastern Cooperative Oncology Group (ECOG) scale, and patients with ECOG 0 and 1 according to their PS were compared with those with ECOG 2, 3, and 4 using the Kaplan-Meier model. Of 118 patients, 60 (51%) had ECOG>1, and 58 (49%) had ECOG≤1. Mean survival time was 19.75±2.26 months (95% confidence interval: 15.28–24.09 months) in ECOG≤1 patients, and 16.19±2.31 months (95% confidence interval: 11.62-20.65 months) in ECOG>1 patients, and no statistically significant difference was observed between the two groups (logrank, Breslow, Tarone-Ware tests: p=0.132, p=0.108, and p=0.111, respectively). Although the p values were not less than the default 0.05 level, we noted all were less than 0.14. PS could not be demonstrated as an independent prognostic factor with multivariate analyzes (Cox PH, Wald: p=0.839).

The laboratory data revealed the followings: The mean survival of patients with normal Hgb levels and those with low Hgb levels were 17.23±2.04 months and 19.37±2.55 months, respectively. There was no significant effect of

**Table 2.** Comparison of limited and extensive stage laboratory values

| Category of variable | Covariate | Unit | Limited + Extensive | Limited Stage | Extensive Stage | p value |
|---|---|---|---|---|---|---|
| Hemogram | Hgb | g/dL | | Normal:12<br>Low:22 | Normal:27<br>Low:52 | 0.909 |
| Biochemistry | LDH | U/L | | Normal:15<br>High:19 | Normal:21<br>High:55 | 0.090 |
| | ALP | U/L | | Normal:27<br>High:7 | Normal:42<br>High:36 | **0.011** |
| | Albumin | g/dl | | Normal:30<br>Low:4 | Normal:57<br>Low:21 | 0.078 |
| | Na | mEq/L | 138.7±3.2 | 139.0±2.7 | 138.7±3.5 | 0.492 |
| Sedimentation | Sedimentation | mm/h | 49.3±28.7 | 48.7±27.8 | 50.9±29.9 | 0.894 |
| Tumor Markers | NSE | mcg/L | 42.4±65.9 | 25.0±20.6 | 48.4±75.2 | 0.257 |
| | CEA | ng/ml | 62.0±153.9 | 2.7±0.8 | 78.3±170.9 | **0.016** |
| | CA 15-3 | IU/ml | 45.6±85.7 | 14.5±0.3 | 46.8±93.5 | 0.112 |
| | CA 125 | IU/ml | 47.8±47.4 | 17.8±5.3 | 58.2±50.9 | 0.083 |
| | CA 19-9 | IU/ml | 395.5±1376.0 | 72.3±94.4 | 497.2±1575.1 | 0.823 |
| | AFP | ng/ml | 4.6±6.9 | 4.4±3.9 | 4.7±7.5 | 0.895 |

Hgb level on survival (p=0.918). The mean survival of patients with normal LDH levels and those with high LDH were 20.11±2.50 months and 16.95±2.27 months, respectively. There was no significant effect of LDH level on survival (p=0.134). There was no significant difference between limited and extensive stages in terms of LDH (Mann-Whitney U; p=0.090). The mean survival of patients with normal ALP levels and those with high ALP were 21.40±2.61 months and 13.85±2.11 months, respectively. There was no significant effect of ALP level on survival (p=0.077) (**Table 3**). Here, we noted the margin of the rejection level the significance. Out of 91 (of 116) patients with normal albumin, 70 (77%) died. Of the 25 with low albumin, 21 (84%) died. The mean survival of patients with normal albumin levels and those with low albumin were 18.97±1.71 months and 11.53±3.28 months, respectively. A very significant effect of albumin level on survival was found (p=0.008). Out of 105 (of 115) patients with normal Na, 80 (76%) died. 9 out of 10 (90%) with low Na died. The mean survival of patients with normal Na levels and those with low Na were 19.05±1.95 months and 11.05±5.90 months, respectively. A significant effect of Na level on survival was found (p=0.046). The mean survival of the patients with normal sediment and those with high sedimentation were 8.19±3.27 months and 20.41±2.53 months, respectively. No significant effect of sedimentation on survival was found (p=0.178).

As for tumor markers: Of the 27 patients whose NSE was analyzed; 3 (60%) of the 5 with normal NSE died and 16 (73%) of the 22 with high NSE died. The mean survival of patients with normal NSE levels and those with high NSE were 40.13±5.83 months and 16.65±3.23 months, respectively. A very significant effect of NSE level on survival was found (p=0.033). The mean survival of patients with normal CEA levels and those with high CEA were 21.66±6.25 months and 14.57±2.82 months, respectively. There was no significant effect of

**Table 3.** The relationship between the clinical and laboratory findings and the survival

| Category of variable | Covariates | Unit | Control values | Mean Survival (months) <with K-M> | p value (1 covariate) <Kaplan-Meier> | p value (>1 covariates)<Cox PH> |
|---|---|---|---|---|---|---|
| Hemogram | Hgb | g/dL | >12<br><12 | 17.29±2.05<br>19.44±2.55 | 0.918 | |
| Biochemistry | LDH | U/L | Normal≤192<br>High>192 | 20.18±2.51<br>17.01±2.28 | 0.134[b] | |
| | ALP | U/L | Normal≤106<br>High>106 | 21.47±2.62<br>13.89±2.12 | 0.077[b] | |
| | Albumin | g/dl | Low≤3.5<br>Normal>3.5 | 19.04±1.72<br>11.57±3.30 | **0.008**[a] | |
| | Sedimentation | mm/h | Normal≤12<br>High>12 | 8.22±3.29<br>20.48±2.54 | 0.178 | |
| | Na | mEq/L | Normal:≥135<br>Low:<135 | 19.11±1.95<br>11.09±5.92 | **0.046**[a] | |
| Tumor Markers | NSE | mcg/L | Normal:<12.5<br>High: >12.5 | 40.27±5.85<br>16.71±3.24 | **0.033**[a] | |
| | CEA | ng/ml | Normal: <3<br>High: >3 | 21.73±6.27<br>14.62±2.82 | 0.194 | |
| | CA 15-3 | IU/ml | Normal: <31<br>High: >31 | 20.63±4.49<br>11.76±4.92 | 0.263 | |
| | CA 125 | IU/ml | Normal: ≤35<br>High: >35 | 25.68±5.28<br>9.43±2.55 | **0.037**[a] | |
| | CA 19-9 | IU/ml | Normal: <37<br>High: >37 | 17.59±3.78<br>14.68±4.62 | 0.766 | |
| | AFP | ng/ml | Normal: <9<br>High: >9 | 11.64±2.21<br>5.44±0 | 0.532 | |
| Other | PS | | ECOG0-1<br>ECOG2-3-4 | 19.75±2.26<br>16.19±2.31 | 0.132[b] | |
| | Stage | | Limited<br>Extensive | 26.91±4.39<br>14.81±1.59 | **0.016**[a] | **0.019** |
| | Sex | | Male<br>Female | 16.92±1.84<br>33.86±5.34 | **0.004**[a] | |
| | Weight loss, kg | | Yes<br>No | 23.27±5.15<br>17.12±1.58 | 0.645 | |
| | Age, year | | Other: <60<br>Elderly: >60 | 19.91±2.01<br>15.22±2.78 | 0.053[b] | |
| | Smoking | | Yes<br>No | 18.24±2.06<br>20.75±3.84 | 0.333 | |
| | CT-receiving | | Yes<br>No | 18.99±1.99<br>13.88±3.76 | 0.407 | |

[a]: Significant at the default 0.05 level; Candidate covariate to be used in the Cox PH model.

[b]: Significant at the 0.15 level; Candidate covariate to be used in the Cox PH model.

CEA level on survival (p=0.194). The mean survival of patients with normal CA 15-3 and those with high CA 15-3 were 20.56±4.48 months and 11.72±4.91 months, respectively. There was no significant effect of CA 15-3 level on survival (p=0.263). The mean survival of patients with normal CA 125 and those with high CA 125 were 25.59±5.26 months and 9.40±2.54 months, respectively. A significant effect of the CA 125 level on survival was found (p=0.037). The mean survival of patients with normal CA 19-9 and those with high CA 19-9 were 17.53±3.76 months and 14.63±4.61 months. There was no significant effect of CA 19-9 level on survival (logrank, Breslow, Tarone-Ware tests: p=0.766, p=0.327, and p=0.476, respectively). The mean survival of patients with normal AFP levels and those with high AFP were 11.60±2.20 months and 5.42±0.00 months, respectively. There was no significant effect of AFP level on survival (p=0.532).

## DISCUSSION

At the time of diagnosis, approximately 2/3 of the patients with SCLC are in the extensive stage and 1/3 are in the limited stage (3). The scattering of patients in our study is also in this direction: 79 (66.9%) of 118 patients were diagnosed in extensive stage and 39 (33.1%) in limited stage. In patients with extensive stage SCLC, all metastatic localizations especially liver, brain, bone marrow, and bone have prognostic importance. The absence of brain and liver involvement stage and the presence of a single metastatic focus in the extensive stage are indicators of better prognosis (5). In our study, out of the 83 patients with extensive stage, 21 of 26 patients with a single metastatic focus died, and 49 of 57 patients with multiple metastases died. The mean survival of patients with a single metastatic focus and those with multiple metastatic sites were 15.33±3.31 months and 13.53±1.50 months, respectively. However, there was no significant relation of the number of metastases on survival. In our study, the most common sites of metastasis were liver (53.8%), bone (37.2%), ipsilateral pleural effusion (32.1%), and central nervous system (24.4%). In our study, the mean survival time was observed as 26.91±4.39 months in the limited stage patients and 14.81±1.60 months in the extensive stage patients, with a significantly longer mean survival in the limited stage patients. In multivariate analyses, stage was found to be an independent prognostic factor.

The effect of age on survival in SCLC is controversial. In the study of Yuen et al., in patients aged 70 years and older, the response and survival rates to combined therapy were similar to younger patients, but toxicity was higher than that of the young (6). Advanced age has been associated with lower PS and more comorbid diseases, often requiring dose adjustment in combination chemotherapy (7). As for our study, the mean survival time of patients under the age of 60 was 19.91±2.01 months, and the mean survival time of patients aged 60 and over was 15.22±2.78 months. Although the relationship of age with prognosis was not statistically significant, the rejection of significance was made with a very small margin which means there is clinical significance.

Female sex has been associated with better response and survival in SCLC (8). The exact reason why women respond better than men is unknown. IIn our study, female patients' mean survival was better than male patients, consistent with the literature.

Wet et al. showed that weight loss is an important variable in prognosis. In that study, there was no difference in average survival between patients without weight loss and those with <10% weight loss, but it was concluded that weight loss was a bad prognostic factor in patients with >10% weight loss (9). In our study, however, no significant relationship was found between weight loss and survival (p=0.645).

The most important known cause of SCLC is smoking, which is detected in approximately 95% of cases (10). Continuing to smoking is a bad prognostic factor. Smokers have more side effects from CT treatment. Smoking increases the morbidity and mortality rates in patients with concomitant COPD and coronary artery disease. Smoking cessation can prolong survival and reduce the risk of relapse (11). In our study, the mean survival of non-smokers was 20.75±3.84 months, and the mean survival of smokers was 18.24±2.06 months. However, the relationship between smoking and survival was not significant.

Rawson et al. reported that PS, serum ALP level, and the disease stage were the most important prognostic factors in a multicenter study conducted with 3873 patients (12). In our study, patients with ECOG 0 and 1 according to PS were compared with those with ECOG 2, 3 and 4. In the univariate analysis, the mean survival time was 19.75±2.26 months in patients with ECOG≤1 and 16.19±2.31 months in patients with ECOG>1, and no statistically significant difference was observed. Here, we noted the margin of the rejection level of the significance. PS could not be shown as an independent prognostic factor with multivariate analyses.

Because SCLC is chemosensitive, its treatment should be started as soon as the diagnosis is made, regardless of the stage. Patients who respond well to CT have a better prognosis. Patients with early relapse after CT have a low chance of responding to second-line therapy and have a bad prognosis. In our study, the mean survival was found to be 18.99±1.99 months in patients receiving CT, and 13.88±3.76 months in patients not receiving CT (13). No significant relation was found

between receiving CT and survival, however, the fact that the mean survival of patients who received CT was clearly higher than the mean survival of patients who did not receive CT, it shows that if the study included more cases, a significant relationship may possibly be obtained, which is consistent with the literature.

The increase in the laboratory parameter LDH was detected in 33%-57% of all SCLC patients and 85% of extensive stage patients, and is a strong predictive and prognostic factor. Increased LDH level is associated with bone marrow involvement. It has been claimed that LDH measurement alone can be used instead of routine bone marrow application because it is a cheap and quick test. In our study, however, no significant difference was found between limited and extensive stages in terms of LDH. Also, there was no significant effect of LDH level on survival. The effect of serum albumin level on survival in SCLC is controversial. In our study, a significant relation was found between albumin level and survival in univariate analysis. Mean survival was 19.04±1.72 months in patients with normal albumin levels, and 11.57±3.30 months in patients with low albumin levels. Anemia is common in patients with SCLC. Cohen et al. suggested that the hemoglobin value during diagnosis is associated with survival (14). In our study, however, no significant relation was found between hemoglobin level and survival in univariate analysis. In the study of Rawson et al. that included 3873 patients, it was shown that serum ALP level is the most important prognostic factor together with PS and stage (12). Elevated ALP is mostly attributed to liver and bone metastases, which are common in SCLC, and therefore to the extensive stage disease. In our study, although there is no significant relationship of ALP on survival, the significance was denied with a small margin. According to Rawson, serum Na level is also one of the important prognostic factors (12). Similarly, in our study, the relation of Na on survival was significant in univariate analysis.

High levels of NSE, one of the tumor markers, are detected in neuroendocrine cells and neurogenic tumors as well as in the serum of patients with SCLC (15). The level of NSE is found to be high at the time of diagnosis in 80% of SCLC patients and is considered a characteristic tumor marker of SCLC. NSE is higher in untreated patients in the extensive stage than in those in the limited stage. Although it provides information about the extent and prognosis of the disease, it is mostly used in treatment follow-up. In our study, NSE appeared as a significant prognostic factor in univariate analysis. CEA has been found to have a predictive value in the prognosis of SCLC in many series. It has been reported that CEA is increased more in metastatic disease, especially in liver and bone marrow metastases (16). In our study, no significant effect of CEA on prognosis was found. It has been reported that the level of CA 125 may increase in NSCLC rather than SCLC, mostly in adenocarcinoma and large cell lung cancer (17). However, in our study, CA 125 had a significant effect on prognosis.

## CONCLUSION

The prognostic value of simple clinical and laboratory parameters before the treatment of SCLC is essential because of the difficulty of detecting small or distant metastases, the expensive, time-consuming, and invasive nature of the staging procedures, and the necessity to start the treatment of SCLC as soon as possible. Eventually, it is known that some clinical and laboratory parameters determine the response to CT, treatment toxicity, and long-term survival. By means of these factors, patients with good prognosis and bad prognosis can be identified and the relevant treatment strategies can be determined. While the aim is to provide long-term survival in patients with good prognosis; it should be to provide maximum palliation with minimum toxicity in those with bad prognosis. Studies on prognostic factors in SCLC are still being conducted, and in the light of these studies, healthier decisions can be made about treatments.

## DECLARATIONS

**Ethics Committee Approval:** Not seeking Institutional Review Board review was in accordance with the policy of Ankara City Hospital since retrospective ethics committee approval is not required for articles that were produced from pre-2020 research data and for doctoral thesis studies.

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**Author contributions:** The manuscript was produced from the specialization thesis of Şimal KÖKSAL CEVHER. Erdal ESKİOĞLU was the supervisor of the thesis. Nuriye YILDIRIM ÖZDEMİR gave valuable insights from the oncological perspective.

**Conflict of interest:** None.

**Informed consent form:** Since the study was a retrospective analysis, no consent was required as per the then-regulations.

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Original Article

# The Evaluation of Kidney Function in Elderly Individuals Under Renin Angiotensin Aldosterone System Inhibitor Therapy

[1]Serhat Küçüker [2]Canan Çiçek Demir [3]Ramazan Demir [4]Vedat Gençer
1.Gunyuzu Sehit Melih Ozcan State Hospital, Department of Family Medicine, Eskisehir, Turkey
2.Atılım University, Faculty of Medicine, Department of Endocrinology, Ankara, Turkey
3.Istanbul Bahcelievler Cumhuriyet Family Health Center, Istanbul, Turkey
4.Kayseri City Hospital, Department of Nephrology, Kayseri, Turkey

**Corresponding author:** Serhat Küçüker, Gunyuzu Sehit Melih Ozcan State Hospital ,Department of Family Medicine, Eskisehir, Turkey
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## ABSTRACT

**Background:** We aim to investigate the impact of hydration status (12-hour fasting or 12-hour water-free fasting) on the estimated glomerular filtration rate (eGFR) and serum potassium in renin-angiotensin-aldosterone (RAAS) blocker users during biochemical assessments.

**Material and Methods:** A total of 90 individuals were enrolled in this longitudinal study. 57 of those were advised to be hydrated for at least 1 L before the next hospital visit. 33 of 90 individuals remained in the non-hydrated group and their blood samples were evaluated following 12-hour fasting. Hypertensive patients were divided according to the antihypertensive medicine group (RAAS blockers, RAAS blockers + diuretics, and others). eGFR, serum potassium, calcium, magnesium, albumin, and glucose levels were compared between hydrated and non-hydrated individuals.

**Results:** The mean age was 48.21±16.59 in hydrated and 47.42±17.12 in non-hydrated groups (p=0.831). Hypertension prevalence was 59.6% in the hydrated group and 54.5% in non hydrated group. In the RAAS blocker users, following hydration, eGFR elevated up to 8-11 ml/dk ($p<0.05$). In the hydrated individuals with age ≥65 years and receiving RAAS blockers, the increment in eGFR was most prominent (p=0.002). Hydration increased eGFR in individuals with RAAS blockers-free and nonhypertensive, however, those increments were not statistically significant ($p>0.05$). Similarly, serum potassium levels decreased following hydration in RAAS blocker users ($p<0.05$). Hyperkalemia (serum potassium ≥ 5 mEq/L) risk decreased from 9.2 fold to 6.16 fold following hydration ($p<0.05$).

**Conclusion:** Twelve-hour fasting is associated with lower eGFR and higher serum potassium levels. An assessment of eGFR and serum potassium following hydration (12-hour water-free fasting) is beneficial for accurately assessing. This impact is more prominent in RAAS blocker users, especially in individuals ≥65 years.

**Keywords:** RAAS blockers, GFR, elderly, hydration, fasting, biochemical assessment

## INTRODUCTION

A fasting of 10-12 hours is believed to be necessary before biochemical screening since it is thought that postprandial lipid components and electrolytes can be quite different from fasting values according to the ingested foods. However, recent data have suggested fasting is not routinely required for a serum lipid profile, electrolyte, and protein level assessment (1-3).

Ensure a fasting interval lasting 12 hours in children and elderly carries some handicap during clinical implementations. While maintaining in children a long fasting interval is very difficult, in elderly individuals, kidney functions can be affected, especially in individuals under the therapy of renin-angiotensin-aldosterone system inhibitor, during a 12-hour of hunger and thirst (4). An unexpectedly low level of estimated glomerular filtration rate (eGFR) can be observed following 12-hour fasting in the elderly and this is a concern for optimizing renin-angiotensin-aldosterone system (RAAS) blocker-

involving therapies when higher dosages are necessary.

In this study, we aimed to investigate the impact of hydration status on a biochemical evaluation for eGFR assessment, and its association with RAAS blocker use, in family medicine polyclinics.

## MATERIAL AND METHODS

*Study Design and Participants*

This longitudinal study was conducted at Gunyuzu Sehit Melih Ozcan State Hospital, Department of Family Medicine between 2018-2019 years. The patients who admitted to outpatient polyclinics due to various complaints were enrolled in the study. On the first visit, the individuals who had no sign of illness (active/chronic infection, acute or severe heart failure, acute kidney injury, cirrhosis, malnutrition, diarrhea) underwent a biochemical analysis including eGFR, following 12-hour fasting. Also, a recent or current nonsteroidal anti inflammatory medicine using was considered for exclusion.

The patients were asked to be hydrated with at least 1 L of water before performing a biochemistry analysis on the next visit (generally within 3 months). The selected patients commonly were on maintenance therapies for hypertension, anemia, thyroid disorders, and preserved heart failure. They were admitting to our polyclinics periodically to reestablish their prescriptions. The clinical features of the participants were noted. Anti-hypertensive medicine users were also noted and divided into subgroups for further analysis (RAAS blockers, RAAS blockers + diuretics, and others). If patients were receiving both RAAS blockers + calcium channel blockers (CCB) and/or alpha-beta blockers, they were included in the RAAS groups. Patients were not instructed specifically for further salt or potassium restrictions during this period. Additionally, participants were divided into two groups according to age; 18-65 years and ≥65 years.

Inclusion and exclusion criteria: Patients who applied to the family medicine outpatient clinic and were required to come for the next control within 3 months were included in the study.

*Laboratory measurements*

We studied the biochemical tests in an in-center laboratory. The samples were studied within 30 minutes following the drawing of blood samples. Serum creatinine, sodium, potassium, magnesium, calcium, albumin, and glucose levels were noted. Serum potassium level above 5 mEq/L was accepted as hyperkalemia. The estimated glomerular filtration rate was calculated by Chronic Kidney Disease Epidemiology Collaboration 2009 (CKD-EPI 2009) equation by utilizing an online website (www.mdrd.com). eGFRs were compared as paired (first registry; eGFR1 and following control; eGFR2).

The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices. Since the study was retrospective a consent form is not available

## STATISTICAL ANALYSIS

Data were analyzed using SPSS (Statistical Package for the Social Sciences) version 23.0. Kolmogorov-Smirnov and skewness and kurtosis tests were used to find the data distribution features. Descriptive data were expressed as mean + standard deviation (SD) and median (minimum-maximum). The paired-Samples T-test was used for the comparison of consecutive longitudinal (before-after) values. Independent-Samples T-test was used for the comparison of the groups. A linear correlation test was used to evaluate the association between parameters. Pearson and Fisher's exact tests were used in the 2*2 Chi-Square analysis of categorical variables. $P < 0.05$ was considered significant at the 95% confidence interval.

## RESULTS

A total of 90 individuals (50 males and 40 females) were evaluated. The mean age was 47.92±16.65 in this cohort. 52 individuals were under antihypertensive therapy. In the hydrated group, 59.6% of the participants (n=31) were receiving RAAS blockers. 17 of those 31 individuals were also receiving diuretics. 57 individuals were referred to be hydrated for the next visit. The clinical and laboratory findings of the participants were given in **Table 1**. Age significantly correlated with eGFR regarding all participants ($p<0.0001$ and $r^2=0.233$). Hypertension prevalence was 57.8 in this cohort; 59.6% in the hydrated group and 54.5% in non hydrated group.

Potassium and eGFR values of hydrated and non-hydrated participants were compared on the basis of antihypertensive medicine use (**Table 2**). The most significant p-value was obtained among RAAS blockers + diuretic users in the paired test both in ages of 18-65 years and ≥65 years. In fact, all groups expressed an improvement in eGFR and potassium levels, however, while some groups reached a statistically significant level the others revealed an improvement that was not statistically significant (Table 2).

Prehydration hyperkalemia risk was higher in RAAS blocker users (p=0.012, OR: 9.20, 95% CI; 1.45 – 58.35), and the risk decreased following hydration (p=0.052, OR:6.16, 95% CI;0.792-48.03). All individuals with post-hydration hyperkalemia were ≥65 years old.

## DISCUSSION

The estimated glomerular filtration rate can decrease over years. Additionally, hypertension and RAAS blockers (especially angiotensin-converting enzyme

**Table 1.** The comparison of the hydrated and non-hydrated patients in regard to clinical and laboratory features

| | Hydrated, n=57 | Non-Hydrated, n=33 | P value |
|---|---|---|---|
| Age, years | 48.21±16.59 | 47.42±17.12 | 0.831 |
| Gender, male/female, n | 32/25 | 18/15 | 0.528 |
| Age groups, n<br>• 18-65 years<br>• ≥65 years | <br>43<br>14 | <br>27<br>6 | 0.602 |
| Anti-hypertensive use<br>• RAAS blockers<br>• RAAS blockers + diuretics<br>• Others (beta and/or alpha-blocker and/or CCB)<br>• None-HT | <br>8<br>13<br>13<br>23 | <br>6<br>4<br>8<br>15 | 0.650 |
| BMI, kg/m$^2$ | 26.35±5.12 | 26.65±3.79 | 0.766 |
| eGFR1, ml/min/1.73 kg/m$^2$ | 79.82±16.39 | 76.78±15.64 | 0.392 |
| eGFR2, ml/min/1.73 kg/m$^2$ | 85.59±16.65 | 78.93±14.67 | 0.060 |
| Potassium1, mEq/L | 4.41±0.31 | 4.37±0.50 | 0.728 |
| Potassium2, mEq/L | 4.11±0.31 | 4.36±0.41 | **<0.001** |
| Sodium1, mEq/L | 137.31±2.73 | 137.00±2.82 | 0.604 |
| Sodium2, mEq/L | 137.64±2.81 | 137.51±2.99 | 0.832 |
| Calcium1, mg/dl | 9.10±0.66 | 9.13±0.67 | 0.789 |
| Calcium2, mg/dl | 9.22±0.67 | 8.96±0.54 | 0.062 |
| Magnesium1, mg/dl | 2.13±0.34 | 2.19±0.38 | 0.485 |
| Magnesium2, mg/dl | 2.26±0.31 | 2.26±0.25 | 0.925 |
| Albumin1, gr/dl | 4.25±0.41 | 4.19±0.36 | 0.496 |
| Albumin2, gr/dl | 4.15±0.39 | 4.31±0.40 | 0.062 |
| Glucose1, mg/dl | 88.49±10.64 | 86.45±8.88 | 0.350 |
| Glucose2, mg/dl | 86.49±10.46 | 89.78±9.61 | 0.121 |

RAAS; renin-angiotensin-aldosterone system, BMI; body mass index, CCB; calcium channel blockers, HT; hypertension, eGFR; estimated glomerular filtration rate (GFR1 first polyclinics registry and GFR2 is the following

[ACE] inhibitors and angiotensin receptor 1 [AT1] blockers) contribute to the development of a lower eGFR in the elderly. The eGFR evaluation following 12-hour fasting in elderly individuals (especially those who are under therapy involving RAAS blockers) carries some negative perceptions (due to lower eGFR) in regard to RAAS therapy optimization. In this study, we have demonstrated that hydrated individuals (hydrated during 12-hour fasting), compared to individuals with 12-hour fasting (water restricted), have significantly higher levels of eGFR and low serum levels of potassium. So, we suggest that the evaluation of kidney functions in elderly individuals be performed in a hydrated status, especially in individuals who are under RAAS blocker therapy.

RAAS is one of the main pharmacological targets for managing hypertension, diabetic nephropathy, and heart failure. RAAS serves as blood volume and arteriolar tone check-point, on a long-term basis. Studies reported that both ACE inhibitors and AT1 receptor antagonists can induce hyperkalemia due to the inhibition of aldosterone secretion and an abrupt acute reversible decline in GFR up to 20-30% at the onset of the therapy (5,6). Due to the decrease in total and extracellular body water by aging, a small amount of water decrement even may carry a critical hazard in maintaining kidney functions (7,8). Additionally, it has been reported that dehydration prevalence is up to 20-30% among older adults (9). Unfortunately, dehydration in the elderly is underdiagnosed due to bland clinical signs and symptoms. Given all these, before screening kidney functions, instructing older individuals to 12-hour fasting will result in lower eGFR, especially when under a RAAS blocker-involving therapy. This study indicates the importance of hydration status in the elderly and hydration can reverse eGFR up to 6-7 ml/min/1.73 m$^2$ in 18-65 years individuals under RAAS blockers therapy. In similar conditions, the recovery of eGFR rises up to 8-11 ml/min/1.73 m$^2$ in individuals > 65 years old. The impact of hydration was independent of being

**Table 2**. The comparison of hydrated and non-hydrated individuals on an age-based view and eGFR and K+ changes following hydrated status.

| | Hydrated, n=57 | |
|---|---|---|
| | 18-65 years (p value) | ≥65 years (p value) |
| RAAS blockers<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | n=5<br>78.00±17.72 vs 84.80±21.34 (0.042)<br>4.70±0.39 vs 4.12±0.19 (0.020) | n=3<br>53.33±10.06 vs 61.66±12.05 (0.002)<br>4.90±0.36 vs 4.25±0.51 (0.023) |
| RAAS blockers + diuretics<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | n=8<br>89.87±11.81vs 96.25±12.91 (0.014)<br>4.51±0.18 vs 4.37±0.24 (0.041) | n=5<br>64.60±20.40 vs 75.00±19.03 (0.002)<br>5.02±0.27 vs 4.20±0.30 (0.003) |
| Other antihypertensives<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | n=10<br>89.00±9.58 vs 90.9±11.34 (0.876)<br>4.01±0.31 vs 4.02±0.22 (0.292) | n=3<br>65.66±20.25 vs 70.66±22.18 (0.090)<br>4.73±0.82 vs 4.30±0.30 (0.385) |
| No-HT<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | N=20<br>82.75±13.11 vs 83.55±14.01 (0.121)<br>4.24±0.39 vs 4.16±0.39 (0.121) | n=3<br>72.00±8.54 vs 79.00±7.81 (0.094)<br>4.30±0.17 vs 4.13±0.28 (0.253) |
| | Non-Hydrated, n=33 | |
| | 18-65 years (p value) | ≥65 years (p value) |
| RAAS blockers<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | n=5<br>72.20±13.02 vs 75.20±14.34 (0.109)<br>4.38±0.68 vs 4.32±0.63 (0.208) | n=1<br>72.00 vs 79.00 NA<br>4.80 vs 4.90 NA |
| RAAS blockers + diuretics<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | n=2<br>75.00±9.89 vs 80.50±10.70 (0.614)<br>4.85±0.77 vs 4.40±0.14 (0.553) | n=2<br>59.50±3.53 vs 60.50±3.53 (0.823)<br>4.35±0.21 vs 4.25±0.49 (0.705) |
| Other antihypertensives<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | n=6<br>61.33±16.80 vs 62.00±16.94 (0.501)<br>4.65±0.41 vs 4.65±0.36 (1.000) | n=2<br>93.50±10.60 vs 94.50±7.77 (0.705)<br>4.35±0.21 vs 4.35±0.07 (1.000) |
| No-HT<br>• eGFR1 vs eGFR2<br>• K1 vs K2 | n=14<br>86.85±9.29 vs 86.42±9.52 (0.742)<br>4.10±0.34 vs 4.20±0.32 (0.072) | n=1<br>61.00 vs 66.00 NA<br>5.30 vs 4.90 NA |

eGFR; estimated glomerular filtration rate, K+; potassium, NA; not applicable

hypertensive since non-hypertensive individuals with ≥65 years exhibited also an elevation of up to 7 ml/min/1.73 $m^2$ in eGFR. However, the recovery in eGFR reached statistically a significant level only in RAAS blockers users. Additionally, potassium levels decrease as well as eGFR following hydration in RAAS blockers users. The improvement was more prominent among individuals > 65 years. Those findings are suggestive of the data indicating prolonged thirst can activate RAAS (thus may contribute to hyperkalemia) (10,11).

Hyperkalemia is a limiting factor in the use of drugs that block RAAS. Hyperkalemia incidence is 7% at the first visit following starting to receive the drug, prevalence reaches 11% in individuals with chronic kidney disease and approximately 45% of hyperkalemia cases are in therapy with ACE inhibitör or AT1 receptor blocker (12). The elderly tend to have hyperkalemia as a result of underlying abnormalities in potassium homeostasis. These include undiagnosed renal dysfunction, tubulointerstitial disease in the kidney, disturbed aldosterone production, and abnormal salt and water balance (13). In community-acquired hyperkalemia among individuals ≥65 years, ACE inhibitors and AT1 receptor blockers increase the risk of hyperkalemia development up to 2.5 times, and if a renal injury is accompanying the risk increases 30-fold (14). Moreover, dehydration and a decrease in urinary concentrating ability contribute to hyperkalemia development in the elderly (4,15). In this study, hyperkalemia prevalence was 11.2% (10.5% in hydrated and 15.2% in non hydrated individuals and p=0.523). In the next hospital visit, hyperkalemia prevalence decreased to 0% among hydrated individuals and remained at 12.1% among non hydrated individuals (p=0.016). The most significant decrease in serum potassium levels following hydration was observed among RAAS blockers users. On the other hand, in a recent study, Wetmore et al. reported that hyperkalemia risk was increased in patients with heart failure, diabetes, CKD, or other comorbid conditions.

The rate of RAAS inhibitor interruption was greater for individuals with heart failure or diabetes mellitus than for those without, while the risk of both interruption and cessation was greater for individuals with advanced stages of CKD than for those without (16). So, the evaluation of those individuals with comorbidities is essential in regard to therapy optimization

The clinical findings of this study have two main implications. First, evaluation of eGFR in RAAS blockers users after 12 hours of fasting without water restriction will provide a higher estimate of GFR and avoid unnecessary dose reduction of RAAS blockers. Second, and most importantly, this approach may increase your suitability for using more aggressive RAAS blockers, especially in people who have the potential to need an aldosterone **a**ntagonist such as spironolactone.

The study's main limitations are the small sample size, the lack of data on hypertension duration and smoking, and single laboratory measurements. The hydration status of participants depended on their statements, so the amount of ingested water may be substantially different from instructed. Moreover, the fasting longevity may be different between patients since the waiting duration and the booking time in polyclinics may affect the duration of blood drawn. A few patients were under spironolactone and/or diuretic therapies, however, the sample size was small and further analysis could not be performed

## DECLARATIONS

**Ethical approval:** This study was carried out in accordance with the Declaration of Helsinki. The study was approved by the Medicana International Hospital Scientific Research Ethics Committee (Date:15.03.2023, Approval number: BŞH-2023/06).

**Declaration of conflicting interests:** The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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Review

# Hepatorenal Syndrome: A Mini Review

Atilla Bulur
Gastroenterology and Endoscopy Private Clinic, Aydın, Turkey

**Corresponding author:** Atilla Bulur, Gastroenterology and Endoscopy Private Clinic, Kurtuluş Mah. 348 Sok. No:56, Nazilli, Aydın, Türkiye
E-mail: atillabulur@hotmail.com
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## ABSTRACT

Hepatorenal syndrome (HRS) is diagnosed in individuals who have no etiologic factors for the development of renal disease other than the chronic decompensated liver disease (DLD). HRS represents the end stage of a series of reductions in renal blood flow caused by progressive severe liver injury. HRS is a strong indicator of morbidity and mortality in these patients. A specific treatment approach for HRS is not available because the mechanisms underlying the development of renal dysfunction are not clear. Because of the severe circulatory abnormality and portal hypertension in the background of the clinical aspect, HRS is the most life-threatening entity in DLD patients with acute renal dysfunction.

**Keywords:** Hepatorenal syndrome, chronic liver disease, kidney failure

## ETIOPATHOGENESIS

The relationship between liver disease and renal failure has been known for more than a hundred years (1-3). Flint noted that in most cases of renal failure in cirrhosis, no significant histologic changes were found in the kidneys at autopsy (3). Hecker and Sherlock in 1956 noted progressive oliguria, very low urinary sodium excretion, and hyponatremia and described nine patients with liver disease in the absence of proteinuria and renal failure (4). In addition, it was found that renal failure was functional in these patients and other patients with chronic renal failure. In these patients, renal failure improved after treatment with liver transplantation.

In 1996, the International Acid Club defined the definition and diagnostic criteria for HRS, and the term is generally accepted for functional renal failure that develops in patients with DLD (1-5). Patients who develop HRS are usually patients with DLD, severe alcoholic hepatitis, or less commonly, patients with portal hypertension due to metastatic tumors and fulminant liver failure from any cause (6-8). Portal hypertension in patients with cirrhosis causes numerous complications. It has been reported that splanchnic vasodilation resulting from portal hypertension plays an important role in renal injury. One of themost important mechanisms is the increase of vasodilators such as nitric oxide in the splanchnic circulation (6,9,10). As cirrhosis decompensates, there is a progressive increase in cardiac output and a decrease in systemic vascular resistance. The second change is thought to be due in part to hypotension-induced activation of the renin-angiotensin and sympathetic nervous systems (7,11) (**Figure 1**).

Bacterial translocation from the intestine to the mesenteric lymph nodes may play an important role in this process (**Figure 1**) (12-15).

## EPIDEMIOLOGY and CLINICAL MANIFESTATIONS

Incidence of HRS, in a prospective study of 229 patients without renal failure with DLD and ascites: HRS developed in 18 percent and 39 percent of patients at one and five years, respectively. Patients with hyponatremia and high plasma renin activity were found to be at the highest risk (12). Usually, HRS develops in patients with advanced cirrhosis, so patients experience other manifestations of chronic liver disease such as jaundice, clubbing, palmar erythema, gynecomastia, temporal wasting, and spider nevus. Also, other clinical features include splenomegaly, bleeding tendency, hepatic encephalopathy, edema, and ascites. Patients usually have lower arterial blood pressure and wider pulse pressure.

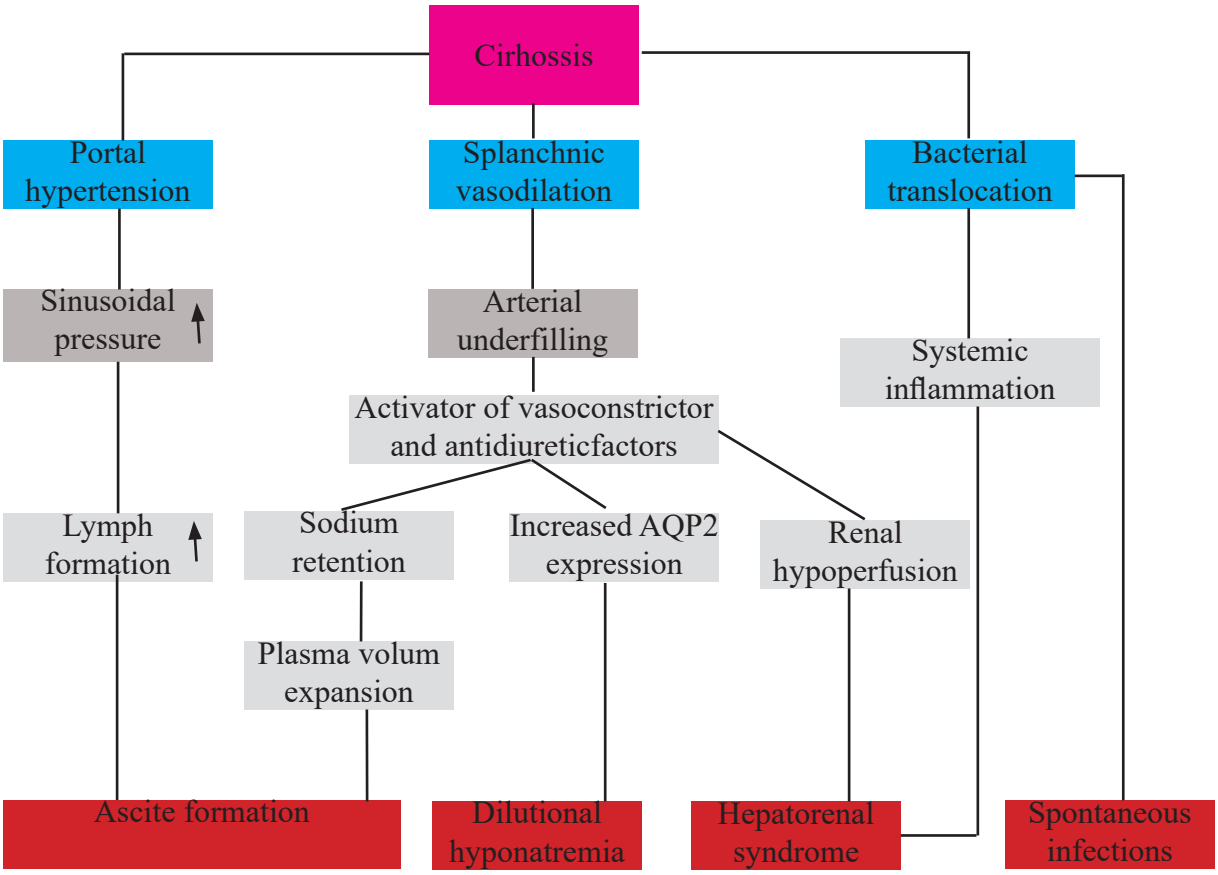


**Figure 1.** Pathogenesis of ascites and related complications of cirrhosis (adapted from reference 14), AQP2;

Urinary output is greatly reduced, especially in type 1 HRS. HRS rarely occurs in patients with early and well-compensated disease. The risk of HRS is increased in patients with refractory acid, defined as unresponsiveness to high-dose diuretics (spironolactone 400 mg daily and furosemide 160 mg daily) (1,5).

## DIAGNOSIS

HRS is characterized by the following features in a patient with DLD (acute or chronic liver disease) (**Table 1**). Many patients with HRS are nonoliguric (especially early in the course of the disease) (6-8).

**Table 1.** Characteristic of hepatorenal syndrome

| |
|---|
| • Progressive increase in serum creatinine |
| • Usually normal urine sediment |
| • No or little proteinuria (less than 500 mg per day) |
| • Low sodium excretion rate (urine sodium concentration is often less than 10 mEq/L) |
| • Nonoliguria or oliguria depending on its severity and duration |

Two forms of HRS have been described, depending on the rate of decline in renal function (5);

**1.Hepatorenal Syndrome Type 1 (HRS-AKI):** This more severe form of HRS is traditionally referred to as hepatorenal syndrome - acute kidney injury (HRS-AKI) or type 1 HRS. It is defined as at least a twofold increase in serum creatinine (sCr) (reflecting a 50 percent decrease in creatinine clearance) to a level greater than 2.5 mg/dL in less than two weeks. GFR is usually less than 20 mL/min. Median survival is less than 2 weeks, and virtually all patients die within 8-10 weeks of the onset of renal failure.

**2.Hepatorenal syndrome type 2 (diuretic-resistant acid):** Type 2 HRS is defined as milder renal dysfunction than is observed in type 1 HRS. The main clinical feature in patients with type 2 HRS is ascites resistant to diuretics. Patients have a longer median survival time of approximately 6 months.

HRS is a diagnosis of exclusion, meaning that patients with DLD must be shown to have no acute or subacute renal injury before the diagnosis of HRS is made. The onset of renal failure is usually insidious, but can be HRS triggered by a bacterial infection (e.g., spontaneous bacterial peritonitis) or gastrointestinal bleeding. At HRS, renal dysfunction may be much more severe than the sCr value suggests. Creatinine is the most practical and common marker for the assessment of renal function. However, assessment of renal function by sCR in cirrhosis is limited because of low muscle volume and impaired formation of creatinine from creatine (synthesized by the liver) in muscle cells and dilute sCr due to excessive water accumulation (16). Because there are several underlying conditions that falsely contribute

to low sCr concentrations in patients with cirrhosis, even in the presence of moderate to severe renal dysfunction, creatinine-based methods often lead to overestimation of true GFR. Even in the presence of moderate to severe renal dysfunction, creatinine-based methods overestimate true GFR by 95% in patients with cirrhosis in published studies (16,17). Therefore, the introduction of a fixed threshold for sCr of 1.5 mg/dl in patients with cirrhosis may not be accurate (5,18). However, this definition may also strongly explain the mortality of cirrhotic patients who die in hospital (19,20).

The Kidney Disease Improving Global Outcome (KDIGO) proposed the acute kidney injury (AKI) criteria by combining the parts of the Acute Dialysis Quality Initiative group for the risk, injury, failure, loss of renal function, and end-stage renal disease criteria (RIFLE) and the Acute Kidney Injury Network group (AKIN) for the AKIN criteria (**Table 2**) (21-23).

Cirrhosis and its complications are summarized in **Figure 1.** Portal hypertension, splanchnic vasodilation, and bacterial translocation are considered the most important pathogenesis factors. One of the complications that develop at the end of this complex cascade is the formation of HRS (15).

## DIFFERENTIAL DIAGNOSIS

The diagnosis of HRS may be made after other causes of acute or subacute renal injury have been excluded. For example, both glomerulonephritis and vasculitis can occur in patients with liver disease and should be suspected in patients with active urinary sediment. Most patients with liver cirrhosis due to obesity with fatty liver have diabetes and may develop diabetic nephropathy. A prospective study examining 562 patients with cirrhosis and renal dysfunction at a single center found that HRS occurred less frequently than prerenal or infection-related renal damage (13%, 32%, and 46%, respectively) (24).

Patients with DLD may develop acute tubular necrosis (ATN) if aminoglycoside therapy, radiocontrast agent therapy, sepsis, or hypotension are present. Suspicion of ATN arises from the history and the rapid rise in sCr as opposed to the normally gradual rise in HRS (5). Some of the conventional laboratory methods used to differentiate between prerenal disease and ATN may not be helpful in patients with cirrhosis. For example, it is associated with fractional sodium excretion of more than 2 percent in ATN and granular and epithelial cells in urinary sediment. On the other hand, in patients with cirrhosis who develop ATN due to renal ischemia, fractional sodium excretion may remain below 1%.

It can be difficult to distinguish hepatorenal syndrome from prerenal azotemia. In patients with cirrhosis, the prerenal disease may be precipitated by gastrointestinal fluid loss, bleeding, or treatment with a diuretic or nonsteroidal anti-inflammatory drug. (6,25)

Beta-blockers are used to prevent varices in patients with DLD. However, these agents can be dangerous in patients with ascites and hypotension, and their discontinuation can lead to the resolution of the overt HRS (26).

## TREATMENT

The most important thing in the treatment of HRS; is the normalization of liver functions, i.e., the treatment of DLD. The ability to avoid alcohol in patients with alcoholic liver disease and HRS improves with follow-up of patients with chronic hepatitis B with antiviral treatments is remarkable (27,28). HRS hepatitis B, especially type 1, was considered a rapid and fatal complication of DLD if liver transplantation could not be performed immediately. Fortunately, as knowledge

**Table 2.** KDIGO, RIFLE, and AKIN AKI diagnostic criteria

| RIFLE | AKIN | KDIGO | Urine Uutput |
|---|---|---|---|
| Risk: sCr increase; 1.5- to 2-fold from baseline or GFR decrease > 25% | Stage 1: sCr increase 1.5-1.9 times from baseline or ≥ 0.3 mg/dl increase within 48 h | Stage 1: sCr increase × 1.5 baseline or GFR decrease > 25% | < 0.5 ml/kg/h for 6-12 h |
| Injury: sCr increase; 2.0-2.9 times from baseline or GFR decrease > 50% | Stage 2: sCr increase > 2- to 3-fold from baseline | Stage 2: sCr increase × 2 from baseline or GFR decreased >50% | < 0.5 ml/kg/h for 12 h |
| Failure: sCr increase; ≥ 3 times from baseline or GFR decrease > 75% or sCr ≥ 4 mg/dl | Stage 3: sCr increased > 300% (>3-fold) from baseline, or ≥ 4.0 mg/dl with an acute increase of ≥ 0.5 mg/dl or on renal replacement therapy | Stage 3: Increase × 3 from baseline or sCr > 4 mg/dl) with an acute rise > 0.5 mg/dl or GFR decreased > 75% | < 0.3 ml/kg/h for 24 h or anuria for 12 h |
| **Loss**:Persistan Acute Kidney Failure: Complete loss of kidney function > 4 weeks | | | |
| **ESKD**: End-stage kidney disease (complete loss of kidney function > 3 months) | | | |

sCr; serum creatinine, KDIGO; Kidney Disease Improving Global Outcomes, RIFLE; The Risk, Injury, Failure, Loss, End-Stage, AKIN; Acute Kidney Injury Network

of the pathogenesis increased, medical treatments were discovered that improved short-term outcomes. In addition, new pharmacological treatments have been developed that improve the feasibility of liver transplantation in eligible patients with HRS (1).

Numerous pharmacological agents have been tried for the treatment of HRS. The use of renal vasodilators (dopamine and prostaglandin analogues) cannot be used because of insufficient data to confirm their side effects and benefits. They are the best pharmacological treatment today, as studies with systemic vasoconstrictors have confirmed a beneficial role at HRS. They were first used in 1998, and their effect is to improve renal function by suppressing arterial splanchnic vasodilation and activating the endogenous vasoconstrictor system (29,30).

If short-term improvement in liver function is not possible, drug treatment should be initiated to try to reverse the acute renal injury associated with HRS. In general, patients who are not candidates for liver transplantation are not followed up in the ICU. Type 1 HRS commonly develops in patients with DLD but can also occur in patients with acute liver failure. Fluid intake, blood chemistry, and urine output must be monitored closely. In case of dilutional hyponatremia, a fluid restriction of 1 liter per day is recommended (31). The use of diuretics in HRS can lead to electrolyte imbalance (hyperkalemia and hyponatremia) and therefore requires very careful evaluation. Patients with type 2 HRS usually have a milder course and can be treated as outpatients.

All antihypertensive agents, including beta-blockers, should be discontinued in patients with HRS. In patients with HRS, treated in the intensive care unit, norepinephrine with albumin is recommended as initial therapy. Norepinephrine is given intravenously as a continuous infusion (0.5 to 3 mg/hour) to increase mean arterial pressure by 10 mmHg, and albumin is given as an intravenous bolus (1 g/kg per day). Intravenous vasopressin may also be effective, starting at 0.01 units/min and titrated as needed to increase mean arterial pressure.

Combination therapy with terlipressin and albumin is recommended for HRS patients who are in the intensive care unit. Terlipressin is administered as an intravenous bolus (1 to 2 mg every four to six hours) and albumin is administered as an intravenous bolus (1 g/kg per day).

In cases where terlipressin therapy is not possible, a combination of midodrine, octreotide, and albumin may be used as initial therapy. Midodrine is given orally (starting at 7.5 mg, increasing to a maximum of 15 mg orally three times daily at 8-hour intervals), octreotide is given either as a continuous intravenous infusion (50 mcg/hour) or subcutaneously (100 to 200 mcg daily), and albumin is given as an intravenous bolus (1 g/kg per day) for two days, then 25-50 g per day until midodrine and octreotide treatment are discontinued.

In selected patients who do not respond to medical treatments, a transjugular intrahepatic portosystemic shunt (TIPS) can sometimes be successful. However, complications associated with TIPS can occur: increased rate of hepatic encephalopathy, deterioration worsening of liver function, renal injury associated with intravenous contrast, and bleeding complications after the complication of procedure (32). For this reason, some clinicians prefer dialysis as the first choice, especially in patients whose sCr remains above 1.5 mg/dL despite medical treatment. Patients with HRS, who develop renal failure, can be treated with renal replacement therapy (hemodialysis or continuous venovenous hemofiltration). In two retrospective studies, 30-50% of transplant candidates who developed acute kidney injury and required dialysis survived following liver transplantation (33,34).

In patients with HRS, acute renal injury is expected to be treated with drug therapy or TIPS. In addition, treatment with norepinephrine, terlipressin, or midodrine plus octreotide aims to increase mean arterial pressure by approximately 10 to 15 mmHg. A systematic review of 501 patients with HRS from 21 studies found a significant association between the increase in mean arterial pressure caused by these vasoconstrictors and the decrease in sCr (35).

Liver transplantation or dialysis treatment is recommended in patients who do not respond to the treatments listed above, whose kidney functions do not improve, and who are candidates for liver transplantation (36,37). The most common liver transplantation indication is DLD, followed by hepatocellular carcinoma and acute liver failure (38,39).

In the 10-year follow-up of 62 patients who underwent liver transplantation due to type 1 HRS, in a single center; While the mean sCr was 3.4 mg/dL before transplantation, it was determined that HRS improved (sCr<1.5 mg/dL) after transplantation and the number of patients who did not need dialysis was 47 (76%). The remaining patients either died or required chronic dialysis (40).

Administration of albumin in patients with spontaneous bacterial peritonitis may prevent the development of HRS, and in patients with acute alcoholic hepatitis, the use of pentoxifylline, a TNF inhibitor, has been shown to reduce the incidence and mortality of HRS compared to the control group (19,41).

Medications such as misoprostol, N-acetylcysteine, and angiotensin-converting enzyme inhibitors have been

tried for the treatment of HRS. No significant treatment response associated with these treatments has been obtained, so they are not recommended. In rare patients, a peritoneovenous shunt is used. Peritoneovenous shunt is the treatment method that provides drainage of ascites from the peritoneum to the internal jugular vein. This therapy has been used in patients with refractory ascites and renal failure due to HRS. In addition, the increase in fluid return to the systemic circulation with shunt therapy may lead to a decrease in the activity of sodium retention and vasoconstrictive mechanisms, and a moderate increase in GFR, respectively (42).

## PROGNOSIS

HRS is a life-threatening complication of DLD. The mortality of patients with liver failure increases significantly if HRS develops. Untreated or unresponsive to treatment, most patients die within weeks of the onset of renal dysfunction. In contrast, some patients with HRS can have their kidney and liver dysfunctions returned to normal with medical, surgical (TIPS, shunt) or liver transplantation (43).

With increasing knowledge of liver cirrhosis, portal hypertension, ascites, as well as HRS, new pharmacological treatments such as terlipressin and albumin administration have proven beneficial in improving the short-term outcomes of HRS. Future treatment of HRS will likely target multiple aspects of the pathophysiological process (1).

Liver transplantation is the definitive treatment for HRS. However, type 1 HRS is an emergency and many patients may die before surgery, as they have a short survival time versus a long waiting time in most centers. If liver transplantation is feasible, the probability of 3-year post-transplant survival in HRS patients treated with terlipressin and albumin is similar to that of patients with cirrhosis without HRS (44).

In a prospective study of 272 patients with cirrhosis; Acute kidney disease developed in 80 patients (29%) within five years. Of these, 42 patients (52%) recovered, and 16 (38%) of these patients had relapsed acute kidney disease. Of all patients, 11 patients with acute kidney disease (14%) progressed to chronic kidney disease and 36 patients (45%) died (45).

## CONCLUSION

HRS is an important cause of morbidity and mortality in patients with chronic liver disease. In cases of renal failure that may develop in these patients, HRS should be kept in mind in the differential diagnosis. HRS treatment can be performed medically (such as terlipressin and albumin), through dialysis, and surgically (including liver transplantation) with success. Therefore, early diagnosis and treatment are very important for the prognosis of the disease.

## DISCLOSURES

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Review

# Rheumatic Diseases and Heart

[1]Serhat Küçüker [2]Melih Pamukcu
1.Günyüzü Şehit Melih Özcan İlçe Devlet Hastanesi, Eskişehir, Turkey
2.Health Sciences University, Ankara Etlik City Hospital, Division of Rheumatology, Ankara, Turkey

**Corresponding author:** Melih Pamukcu, Varlık Mahallesi, Halil Sezai Erkut Caddesi Yenimahalle, Ankara, Turkey
E-mail: melihpamukcu@yahoo.com
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## ABSTRACT

Rheumatic diseases may increase the risk of developing several cardiovascular comorbidities. The increased cardiovascular disease risk in patients with systemic rheumatic diseases is conditioned, partially, by the presence of cardiovascular risk factors such as age, gender, family history, smoking, sedentary lifestyle, and dyslipidemia. However, the inflammatory nature of rheumatic diseases, the shared pathophysiological pathways, and the side effects of antirheumatic therapies have an association with cardiac events. Early diagnosis and treatment are the main key points in preventing future comorbidities.

**Keywords:** Rheumatoid arthritis, ankylosing spondylitis, cardiac involvement, vasculitis, psoriatic arthritis

## INTRODUCTION

Rheumatic diseases are generally examined in three different classes; joint diseases, autoimmune connective tissue diseases, and vasculitides. They progress with significant cardiac involvement in all three groups. Cardiac involvement may present in a spectrum ranging from asymptomatic, mild, or subclinical to serious disease with a risk of mortality and morbidity. Cardiac manifestations in rheumatic diseases are frequently encountered as pericardial, myocardial, and endocardial involvement, atherosclerosis and ischemic heart disease, cardiomyopathy, heart failure, or cardiac conduction system involvement that may cause arrhythmias. This review aims to discuss the impact of main rheumatologic diseases on the heart.

### Rheumatic Joint Diseases

**Rheumatoid arthritis:** The most common chronic inflammatory polyarthritis is rheumatoid arthritis (RA). It mostly occurs between the 4th and 6th decades. Its incidence in the community varies between 0.5-1% and is observed approximately 3 times more frequently in women. Inflammatory involvement of the joints and cardiovascular complications are important causes of morbidity in these patients. Symmetrical involvement of three or more joints (usually hand and foot joints) is a disease characterized by >90% rheumatoid factor positivity and 80-90% anti-citrulline cyclic peptide antibody positivity and an increase in acute phase reactants. Besides heart and vascular involvement, eye, lung, and kidney involvement are also observed (1). Today, ischemic heart diseases and heart failure secondary to coronary atherosclerosis are the most common causes of mortality in this group of patients. The most common form of cardiac involvement is pericarditis. Pericardial effusion is frequently seen on echocardiography (ECHO) and is seen in approximately 35-40% of patients. In addition, nodules in the heart valves, tricuspid regurgitation, aortic stenosis, mitral regurgitation, mitral and aortic valve thickening/calcifications, mitral valve prolapse, atrial fibrillation and prolonged QT interval can be found in the electrocardiogram. While myocarditis and myocardial fibrosis related to RA are less common, cardiac amyloidosis is rare. Changes in the heart valves usually cause an asymptomatic clinic. Patients with a diagnosis of RA present to the cardiology outpatient clinic with symptoms of cardiac pump failure and advanced heart failure. The incidence of heart failure in patients with RA over 80 years of age is 36%, which means that heart failure is twice as high as in individuals of similar age without a diagnosis of RA (2-4). While the cause of heart failure in individuals over 80 years without a diagnosis of RA is 77% of classical cardiovascular risk factors,

this rate is 54% in patients with a diagnosis of RA. This difference may be due to other risk factors associated with RA, such as myocarditis or heart valve disease (4).

The risk of AF is slightly increased in RA patients (3-4%), and it has no effect on mortality. Prolongation in the QT interval, which is a parameter that can be used to predict the risk of cardiovascular mortality, is observed in 48% of patients with RA, and this is more common than in the normal population (5).

**Spondyloarthritis (Ankylosing spondylitis, psoriatic arthritis, reactive arthritis):** Spondyloarthropathies are a group of diseases that share similar clinical symptoms and findings and similar genetic predispositions to the family of inflammatory rheumatological diseases. This group of diseases is divided into subgroups diseases according to their clinical presentations, and the most common one is ankylosing spondylitis (AS), also known as Bechterew's disease (6). Other subgroup diseases are psoriatic arthritis with a psoriatic picture and reactive arthritis with inflammatory bowel disease or infections. Psoriatic arthritis often progresses with peripheral joint involvement. Other typical organ involvements are the eye (often anterior uveitis) and less commonly the heart.

Typically in ankylosing spondylitis, aortitis, aortic regurgitation, myocardial fibrosis, coronary artery disease, aortic lump formation in the aorta adjacent to the mitral anterior valve, left ventricular dysfunction and heart failure, cardiac conduction system disorders (2nd and 3rd degree atrioventricular [AV] blocks, ventricular involvement such as early beats can be observed) (7). Additionally, the increased risk of mortality in ankylosing spondylitis is primarily associated with cardiovascular involvement. The standardized death rate in these patients is slightly higher in men than in women, and 40% of these deaths are due to cardiovascular causes (8). The pathoanatomical findings of ankylosing spondylitis involve subaortic structures such as ascending aorta and aortic root involvement, membranous part of the interventricular septum, or involvement of mitral anterior valve that may cause mitral regurgitation can be observed (9). Likewise, cardiac conduction system disorders are frequently observed in patients with AS (10). Although aortitis is not observed very frequently nowadays, it can be observed in combination with typical aortic regurgitation due to aortic valve involvement in AS patients. The frequency of aortitis varies between 3-18%, depending on the age and duration of the disease. Therefore, AS patients frequently go to aortic valve surgery as valve surgery (11). Histologically, focal destruction of the media layer of the aortic wall is accompanied by the histopathologically characteristic feature of aortitis, which is a thickening of the intimal and adventitial layers and resulting vascular narrowing. Fibrotic thickening of the aorta and aortic valve may progress under the valve over time and cause a subaortic lump. The frequency of severe cardiac conduction disturbance, especially high-grade AV block, and severe bradyarrhythmias, was observed in AS with a frequency of 5%. This outcome was associated with HLA (Human Leukocyte Antigen) B27 positivity, and in most cases with HLA-B27 positivity, involvement of the AV node was observed and mostly a pacemaker was needed. The risk of AV block may also occur in healthy individuals with HLA-B27 positivity and aortic insufficiency (10). In addition, HLA-B27 positivity was observed at a higher rate in those with pacemakers than in normal individuals (12).

In psoriatic arthritis, unlike AS, the prevalence of cardiac conduction defect or valve involvement did not increase compared to the normal population. While disorders due to HLA-B27-related aortic valve and AV node involvement that develop after streptococcal infection are now defined as reactive arthritis, they were called Reiter's syndrome in the past. Cardiac involvement and acute rheumatic fever in reactive arthritis are less common in developed countries than in developing and underdeveloped countries (13).

There are limited data on cardiovascular, gastrointestinal, or renal risks associated with using non-steroidal anti-inflammatory drugs (NSAIDs) in treating patients <50 years of age with a diagnosis of AS or psoriatic arthritis. These risks have been observed more commonly among elderly individuals. Heart failure, kidney failure, or a history of peptic ulcer are predisposing factors for the development of NSAID-related complications. Except for those mentioned, no increase in risk has been observed with short-term or continuous high-dose NSAID use (14). The results of two independent studies conducted on AS patients, increased mortality was observed with low-dose NSAID intake rather than with those taking high-dose NSAIDs (8,15). These results suggest that NSAID use may be beneficial in patients with chronic inflammatory disease, after considering and evaluating other risk factors.

## Autoimmune Connective Tissue Diseases

Idiopathic inflammatory myopathies (IEM) such as systemic lupus erythematosus (SLE), scleroderma (progressive systemic sclerosis (PSS), dermatomyositis and polymyositis, and mixed connective tissue disease are diseases in this group that can involve all layers of the heart. The diagnosis of this group of diseases is made by the presence of autoantibodies (such as antinuclear antibody [ANA], extractable nuclear antigen, and anti-double-stranded DNA) together with the findings of extracardiac involvement such as skin and joint involvement.

The prevalence of myocarditis is 10% in SLE and PSS, and

25% in IEM (16). The earlier echocardiographic finding of myocarditis is usually a regional wall motion defect. The gold standard diagnostic method for myocarditis is an endomyocardial biopsy. Regional edema, late-phase involvement, and wall motion defect detected in cardiac magnetic resonance (MR) imaging (which is a non-invasive method) helps to diagnose myocarditis at an early stage. Cardiac involvement in PSS can progress with myocardial fibrosis together with myocarditis. Poor prognosis can be observed in patients due to the presence of myocardial fibrosis, arrhythmia, and right heart failure secondary to pulmonary hypertension, which is known as 'scleroderma heart disease' (17). A right heart catheterization will be useful in guiding the diagnosis and treatment of pulmonary hypertension in those individuals.

Pericarditis can be observed in any connective tissue disease. It is most frequently observed in SLE, with a frequency of 25-39%. Mitral valve involvement is typically observed as nonbacterial verrucous endocarditis (Libman-Sacks) in SLE. Antiphospholipid antibody levels should be measured to detect these valvular deposits associated with SLE. It has been determined that there is an increased risk of congenital complete AV block in pregnant women with the presence of anti-SS-A/Ro autoantibodies, and this conduction system defect is permanent in a few (2%) cases (18).

**Vasculitis**

Vasculitic autoimmune diseases are characterized by partial or complete ischemia, necrosis or bleeding of blood vessel walls, in a manner of cellular inflammation. Anti-neutrophil cytoplasmic antibodies (ANCAs) can be found in granulomatous polyangiitis (GPA or Wegener's disease), microscopic polyangiitis, and some eosinophilic granulomatous polyangiitis (EGPA/Churg-Strauss disease). In the cases of giant cell arteritis (Horton's disease) and Takayasu arteritis (TA) ANCAs are absent. Cardiac involvement can be seen with a frequency of 5-25% in systemic vasculitides. Pericarditis, myocarditis, endomyocardial fibrosis, coronary ischemia due to vasculitis, valve insufficiency, and arrhythmias may occur as a result of cardiac involvement.

Malignant hypertension is common in polyarteritis nodosa (PAN), which is more common in chronic hepatitis B (HBV) patients. Compared to giant cell arteritis, cardiac findings such as aortic insufficiency, aortic aneurysm, vasculitis-related ischemia, and pump failure can be seen in TA, often at younger ages (19).

### Other Rheumatological Diseases

Still's disease is less frequent and its typical findings are polyserositis and fever, and pericarditis frequently occurs (20-30%). In Behçet's disease, cardiac involvement is between 7-46% and generally causes pericarditis. Constrictive pericarditis, which can sometimes cause hemorrhagic tamponade, is also seen. Again, in more than half of Behçet's patients, intracardiac thrombus formation (often in the right atrium) is the first manifestation (20,21). Coronary vasculitis and aortitis causing aortic aneurysm and aortic regurgitation can be found in Behçet's patients and cardiac surgical aortic valve replacement may be necessary in some cases. Although secondary amyloidosis is seen less frequently in rheumatic diseases due to inadequate treatment or long-term development, AA type amyloid deposits can cause heart failure (22,23).

## CARDIOVASCULAR COMORBIDITY IN RHEUMATOLOGICAL DISEASES

All-cause mortality, myocardial infarction rate, heart failure, and ischemia-induced revascularization rate are more prevalent in RA compared to other rheumatologic diseases (24). Additionally, 80% of RA patients have at least one classic cardiovascular risk factor. Arterial hypertension is observed with a frequency of 57% in RA patients (25). The incidence of cardiovascular events has also increased in AS and psoriatic arthritis. The risk of mortality in AS is increased due to the presence of cardiovascular morbidity and multiple risk factors (26).

In patients with connective tissue disease, the atherosclerotic process progresses faster and may cause myocardial infarction at earlier ages. Atherosclerotic vasculopathy is observed more frequently in this group of patients due to innovations in treatment and increased life expectancy due to conditions. Although classical cardiovascular risk factors are responsible for approximately half of the cardiovascular diseases in these patients, the treatment of cardiovascular risk factors plays an important role in reducing mortality and morbidity. Early diagnosis is important in cardiac involvement of some rheumatic diseases such as SLE, and computed tomography is a useful method for detecting calcium deposits. Cardiac MRI is the best method for detecting inflammatory changes (27).

It has been reported that the use of statins in the treatment to reduce CV morbidities reduces mortality in RA patients. It has also been suggested that the use of high-dose statins reduces the risk of developing RA (28).

## MANAGEMENT OF CARDIOVASCULAR DISEASES IN RHEUMATOLOGICAL DISEASES

Diagnostic tests should definitely be requested in cardiovascular involvement of rheumatological diseases, especially in the involvement of diseases such as SLE and polymyositis, such as pericarditis and myocarditis. Routine echocardiography should be performed annually to detect early pulmonary hypertension and heart failure in some autoimmune diseases such as scleroderma. In

addition, NT-pro BNP measurement in controls will also help in diagnosing heart failure in these patients (29). Likewise, ECHO should be performed every 1-2 years in the early detection of aortic valve disease that may occur in AS patients. The main treatment in direct inflammatory involvement of rheumatological diseases such as pericarditis, myocarditis, and vasculitis is high-dose glucocorticoid therapy and antirheumatic drugs such as methotrexate, and azathioprine. Methotrexate is one of the rare drugs proven to increase survival by reducing cardiovascular mortality in RA patients. A good response is obtained from new-generation drugs such as tocilizumab and rituximab, which are used in severe cases (30-33). Conventional treatment methods used in cardiology are used in practice for other cardiac conditions and comorbidities in rheumatologic diseases.

## CONCLUSION

Cardiac involvement is a consequence of systemic inflammation which occurs in RA, AS, SSc, and SLE with different prevalences and is commonly silent. Inflammatory rheumatic diseases can affect all cardiac structures; the myocardium, cardiac valves, pericardium, conduction system, and arterial vasculature. The increased risk of cardiac mortality, prevention of comorbidities, and surveillance is crucial in patients with rheumatic diseases.

Early diagnosis and effective management of cardiac involvement are essential in inflammatory rheumatic diseases. Electrocardiographic and echocardiographic assessments should also be executed as routine evaluations.

## DISCLOSURES

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Review

# Principles of Bariatric Surgery

[1]Gülçin Türkmen Sarıyıldız [2]Canan Çiçek Demir
1.Atılım University, School of Medicine, Medicana International Ankara Hospital, Department of General Surgery, Ankara, Turkey
2.Atılım University, School of Medicine, Medicana International Ankara Hospital, Department of Endocrinology, Ankara, Turkey

**Corresponding author:** Canan Çiçek Demir, Atılım University, School of Medicine, Medicana International Ankara Hospital, Department of Endocrinology, Ankara, Turkey
E-mail: canancicek@hotmail.com
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## ABSTRACT

This mini-review appoints on the mechanisms linking bariatric surgery and the logic of weight loss by addressing various types of procedures in individuals with obesity. The essential approach for bariatric surgery for the purpose of achieving satisfactory weight loss involves the determination that, obesity is a disease associated with multiple adverse events on human health which can be reversed or improved by successful weight loss following bariatric surgery in individuals who have failed to achieve weight loss by non-surgical treatment options. Here we summarize different types of bariatric surgery and their clear differences.

**Keywords:** Bariatric surgery, sleeve gastrectomy, gastric mini bypass, obesity

## INTRODUCTION

In ancient times, obesity was not a health problem, but a sign of wealth, health, beauty, and fertility. Obesity, which is defined as abnormal and excessive fat accumulation in the human body, is a chronic disease of our age that is increasing in prevalence all over the world and adversely affects many systems in the organism. Early diagnosis of endocrine disorders that may cause obesity is important to prevent the overtreatment of obese individuals. In the treatment of exogenous obesity, there are corrections of environmental factors, diet, regular physical activity, lifestyle changes, and medical treatment options. Surgical treatment is considered in patients who cannot achieve successful weight loss and weight control as a result of all these. Although surgical treatment is the final treatment method to be preferred, paradoxically, it appears as the treatment option that provides the most permanent weight control and has more promising long-term results (1). It should be kept in mind that it will be useful to be known as an adjunct tool in the treatment of complicated obesity. The aim of surgery should be to provide effective weight control with the most physiological method possible.

## DEFINITIONS and CLASSIFICATION

Body mass index (BMI) is calculated using weight in kilograms divided by the square of height in meters (kg/m2). Today, the standard screening and monitoring tool for obesity is the measurement of body mass index (BMI). A universal classification for BMI has been offered by the World Health Organization and many studies have been conducted on this definition and classification system (2).

Underweight: less than 18.5 kg/m²

- •Normal range: 18.5 kg/m2 to 24.9 kg/m²
- •Overweight: 25 kg/m2 to 29.9 kg/m²
- •Obese, Class I: 30 kg/m2 to 34.9 kg/m2
- •Obese, Class II: 35 kg/m2 to 39.9 kg/m²
- •Obese, Class III: more than 40 kg/m²

## BARIATRIC SURGERY INDICATIONS

In the treatment of obesity, bariatric surgery, which is also called metabolic surgery, has been applied with increasing frequency in recent years. A multidisciplinary approach, appropriate patient selection, adequate preoperative evaluation, and appropriate postoperative follow-up are very important for the success of the surgery and to achieve minimized acceptable morbidity and mortality rates. Indications for bariatric surgery can

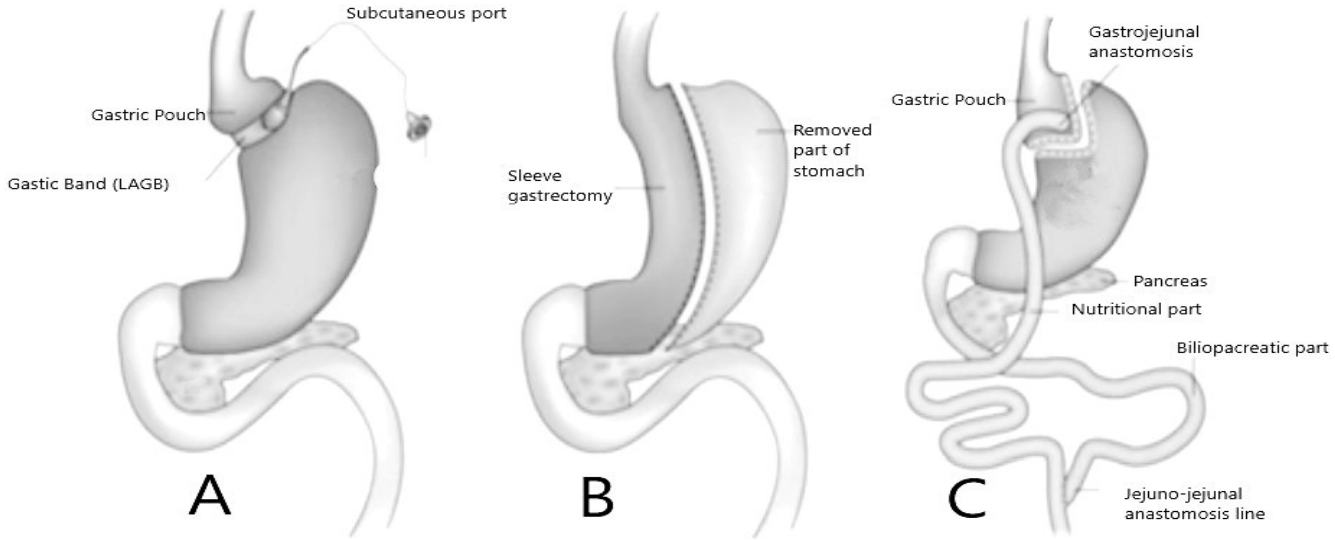


**Figure 1A.** Adjustable gastric band. (Adapted from references 4,5)

be listed as follows;

• To have the ability to understand the surgical procedures to be applied and to evaluate the benefits and possible complications of the surgeries

• Body mass index (BMI) >40 kg/m2

•Body mass index (BMI)>35 kg/m2 and accompanying type 2 diabetes, hypertension, dyslipidemia, sleep apnea, arthritis

• Patients with body mass index (BMI) >30 kg/m2 and uncontrolled type 2 diabetes, which has been shown by increasing studies in recent years

• Adherence to lifestyle changes to be applied in the postoperative period

• Being between the ages of 18-68: Although there is an age limit, there may be differences in the age range according to the performance status of the patients.

## BARIATRİC SURGERY TECHNIQUES

Bariatric surgery techniques are surgical techniques that can be performed by open, laparoscopic, robotic, or endoscopic methods, which restrict food intake by reducing the stomach volume, shortening and/or bypassing the intestinal segment where the ingested food will be absorbed, or provide weight loss by combining both methods. Briefly, it can be grouped under two main headings restrictive and malabsorptive.

### Restrictive Techniques

**An adjustable gastric band (LAGB, lap band):** It was first used in morbid obesity surgery in 1993 and is still being used in the USA with FDA approval since 2001 (3). In this method, a gastric pouch of approximately 30 ml is created by placing a silicone band 2-3 cm below the gastroesophageal junction (**Figure 1A**) (3,4). In this way, the patient's early feeling of satiety is ensured and less caloric intake is realized. It is the most physiological surgical procedure because there is no need for any resection, diversion, or bypass procedure in the stomach or intestinal system. Weight control is attempted by inflating and deflating the silicone band around the stomach with the help of a fully reversible port placed under the skin when desired. With this method, the rate of extreme weight loss (Excess Weight Loss: EWL), which is accepted as an indicator of surgical success, is not as high (usually as much as 50%) as the achieved weight loss following sleeve gastrectomy and gastric bypass surgery (50-70%). However, this method is still used in the USA because it does not require resection. However, it is a method that has begun to be abandoned in Europe and many parts of the world.

**Sleeve gastrectomy:** It was previously used as a first-line surgery in patients with a very high body mass index to reduce excess weight and reduce complications associated with prolonged surgery before surgeries such as Roux en-Y gastric bypass (RYGB), biliopancreatic diversion - duodenal switch (BPD-DS) (6). Due to the effective weight loss and good metabolic results observed in the postoperative period in following periods, sleeve gastrectomy was started to be performed as the primary surgery by Canadian surgeon Michel Gagnier (4) (**Figure 1B**). Today, laparoscopic sleeve gastrectomy (LSG) has become a safe and effective primary bariatric surgical method with high popularity and increasing frequency for surgeons and patients. The success of the surgery is based on creating a tubular stomach with the appropriate technique and leaving no gastric fundus part behind. Although EWL rates are 60-70% at the end of 2 years, weight regain is seen at 55-60% rates after 5 years (7).

### Malabsorptive Techniques

Roux En Y gastric bypass: It is the most frequently performed bariatric surgery technique in the world, especially in the United States (8). It provides effective weight loss with its restrictive effect with the gastric pouch of 10-30 ml volume formed in the stomach

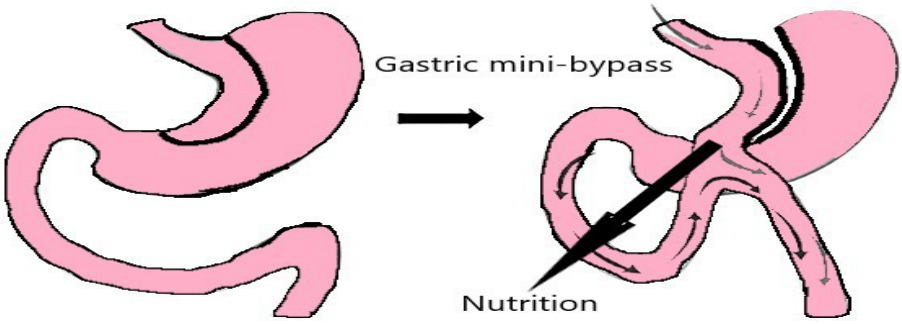


**Figure 2.** Mini gastric bypass. Retrieved from Mahawar et al. (11)

section below the gastroesophageal junction and by reducing food absorption by bypassing a part of the duodenum (**Figure 1C**). Since a certain part of the small intestine is bypassed, the total length of the intestine where food is digested and absorbed is shortened; thus, the amount of calories and fat taken with the surgically created malabsorption is reduced. Due to a number of intestinal hormones secreted due to the newly formed digestive tract, hunger is suppressed, the patient feels satiated, and it is observed that type 2 diabetes is treated by regulating sugar metabolism (9). With this bariatric procedure, patients can lose 60-80% of their excess weight (EWL). The disadvantages are that weight regain is low compared to sleeve gastrectomy but relatively high compared to other procedures, and the risk of internal herniation because more than one anastomosis is required.

**Mini gastric bypass -single anastomosis gastric bypass:** This technique was developed by Dr. Robert Rutledge in 1997. In fact, this technique is based on the Billroth 2 gastrojejunostomy logic, which is performed following stomach ulcers and stomach cancer in the past years (10). A 20 cm gastric pouch is prepared along the long axis of the gastric minor curvature under the guidance of the intraluminal gastric tube, and the procedure is completed by performing a gastrojejunostomy anastomosis 150-200 cm distal to the ligament of Treitz (**Figure 2**). It is an effective surgical method that is in restrictive and absorption-reducing features. While performing it with a single anastomosis technique is superior to RNY, intestinal gastric bile reflux that may develop afterward is seen as a disadvantage of the procedure. In recent years, this surgical procedure, the frequency of which has been increasing all over the world, is increasing in popularity in terms of the short operation time, easy application, weight loss equivalent to other methods, and resolution of comorbidities.

**Biliopancreatic diversion ± duodenal switch:** The biliopancreatic diversion was first described by Scorpinaro et al. in 1979 (12) (**Figure 3**). This surgery consists of a horizontal gastric resection with the closure of a duodenal stump, gastroileal anastomosis, and an ileoileal anastomosis, to form a 50 cm common channel and a 250 cm alimentary channel.It is the least frequently performed bariatric surgical procedure today. It has a limited application area in patients who are super obese (BMI >60 kg/m2) or in cases where revision is required after the first surgery. It is one of the surgeries that most disrupt physiology (13). Complications can include serious nutritional losses, diarrhea, and conditions that impair quality of life such as steatorrhea. It is recommended that this technically

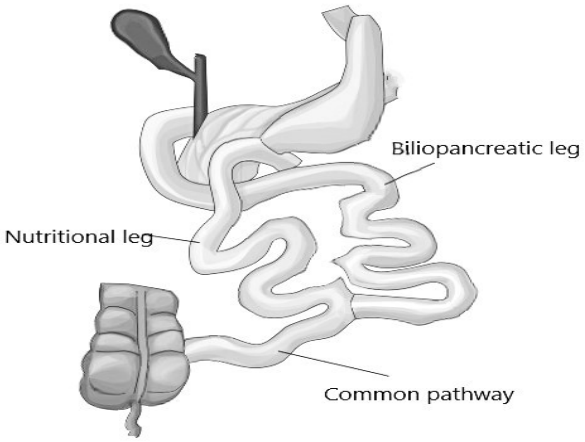


**Figure 3.** Biliopancreatic diversion and duodenal switch (Adapted from reference 12)

difficult procedure be performed in centers with suitable technical infrastructure, high patient volume, and by experienced surgeons (14).

### Conclusion and Look to the Future

The rates of obesity and diabetes mellitus are growing among all ages of the population, especially among young adults. As the population becomes more obese and access to weight loss procedures becomes more accessible, it is clear that the number of bariatric surgical operations will increase in the future. It is a debate whether bariatric surgery is the solution to the problem and whether bariatric surgery should not be considered a treatment for obesity-related morbidities. However, lifestyle intervention has modest improvements in long-term outcomes in obesity, so bariatric surgery is becoming increasingly attractive. However, justifying this procedure for obesity treatment requires stronger evidence given the potential complications and recurrence of obesity.

## DISCLOSURES

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# A Rare Complication in a Peritoneal Dialysis Patient: Hydrothorax in Late Period

[1]Tamer Selen [2]Çise Tüccar [3]M. Deniz Ayli
1.Düzce Atatürk State Hospital, Nephrology Department, Düzce, Turkey
2.Health Sciences University, Department of Chest Diseases and Tuberculosis, Diskapi Yildirim Beyazit Education and Research Hospital, Ankara, Turkey
3.Health Sciences University, Ankara Etlik City Hospital, Nephrology Department, Ankara, Turkey

**Corresponding author:** Tamer Selen, Düzce Atatürk State Hospital, Nephrology Department, Düzce, Turkey. E-mail: tamer_selen_@hotmail.com
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## ABSTRACT
Peritoneal dialysis (PD) associated hydrothorax is a rare complication caused by leakage of dialysis fluid from the peritoneal cavity into the pleural space. The typical clinical presentation is a right-sided pleural effusion and patients present with sudden chest pain, shortness of breath, and loss of ultrafiltration. The fluid is usually transudate. Chow gradient [pleural fluid glucose concentration - serum glucose concentration] > 50 mg/dL supports the diagnosis. It usually occurs in the first few months after the onset of PD in cases with congenital diaphragmatic defects or lymphatic drainage disorders. In patients with clinical conditions that increase the pleuroperitoneal pressure difference, such as constipation, may also occur in later periods, as in the case we presented. A 53-year-old male patient presented with chest pain and shortness of breath in the 10th month of PD treatment. A diagnosis of "PD-associated hydrothorax" was made with transudative pleural effusion in the right hemithorax and high a Chow gradient. In this case, increased pleuro-peritoneal pressure difference due to constipation that has been going on for several weeks was evaluated in favor of a late hydrothorax clinic.

**Keywords:** Peritoneal dialysis, pleural effusion, hydrothorax

## INTRODUCTION
Peritoneal dialysis (PD) associated hydrothorax is a rare complication caused by leakage of dialysis fluid from the peritoneal cavity into the pleural space and was first described by Edward and Unger in 1967 (1). Cases due to congenital diaphragmatic defects or lymphatic drainage defects occur predominantly in the right hemithorax and usually within the first few months after the onset of PD (In more than 50% of cases within the first three months) (2,3). On the other hand, sudden coughing attacks, constipation, tight clothing, and an increase in intra-abdominal fluid volume may also lead to the development of hydrothorax even in later periods through an increased pleuro-peritoneal pressure difference (4,5).

Hydrothorax may be completely asymptomatic or result in pleuritic chest pain, shortness of breath, and loss of ultrafiltration.

In this article, we present a case of PD who applied with chest pain and shortness of breath at the 10th month of PD treatment and was diagnosed with PD -related hydrothorax in the late phase.

## CASE
A 53-year-old man was admitted to our emergency department with increasing shortness of breath and right chest pain. Blood pressure was 100/75 mmHg, body temperature was 36°C, heart rate was 96 beats/minute, respiratory rate was 20/minute, and oxygen saturation on room air was 95%. There was no pretibial edema on physical examination. Breath sounds and chest vibration were decreased; percussion was dull in the lower right lung segments. Laboratory findings: urea: 89 mg/dL, creatinine: 7.02 mg/dL, albumin: 3.9 g/dL, hemoglobin: 11.7 g/dL, white blood cell count: 8800/mm$^3$, C-reactive protein: 9.05 mg/dL. On anteroposterior chest X-ray, the increased density in the lower right lung area was evaluated as pleural effusion (**Figure 1A**), and he was hospitalized.

Peritoneal dialysis was started 10 months ago with a diagnosis of chronic renal failure due to arterial hypertension. Because of good residual renal function,

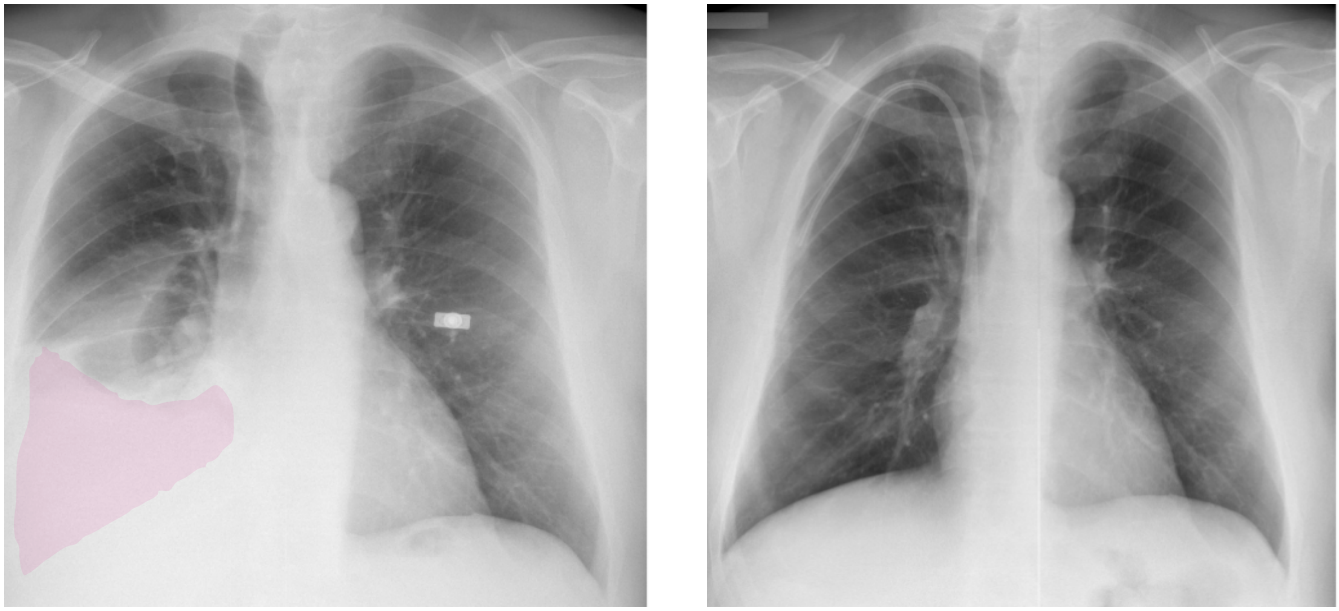

**Figure 1.** A) Right pleural effusion on chest X-ray is illustrated, B) Chest X-ray at the end of 1st week. .

he was prescribed nocturnal intermittent peritoneal dialysis with a cycler. He performed 4 night cycles with an inflow volume of 1900 ml with a lactate-buffered dialysis solution containing 1.36% glucose. The peritoneal membrane had a high average permeability, and there were no problems with adequacy parameters.

The patient has been suffering from constipation for several weeks. Last week's records indicated a decrease in ultrafiltration volume of 100-300 ml/day. The patient has no known pre-existing heart failure. Diagnostic thoracentesis in the right hemithorax revealed 70 leukocytes and 50 erythrocytes in the straw-coloured fluid. There was no growth in culture and no malignant cells in cytology. The fluid was transudative according to Light criteria (**Table 1**). The Chow gradient [glucose concentration in pleural fluid (665 mg / dL) - serum glucose concentration (131 mg / dL)] was calculated to be 534 mg/dL. The high chow gradient (> 50 mg/dL) supported the diagnosis of hydrothorax associated with PD and PD was suspended. One week after starting hemodialysis, the dyspnea resolved completely, and the effusion disappeared on chest X-ray (**Figure 1B**). The patient did not want to continue PD and refused diagnostic procedures such as scintigraphic examination. The PD catheter was removed and a maintenance hemodialysis program was initiated.

## DISCUSSION

This article presents a relatively late case of hydrothorax associated with PD. It was suspected that the increase in intra-abdominal pressure due to constipation, which persisted for several weeks, led to the development of PD -related hydrothorax in the late phase.

Our patient was diagnosed on the basis of the results of physical examination, chest X-ray findings, and biochemical analysis of the fluid. The detection of transudative fluid with high glucose content is very important for the diagnosis. A glucose concentration in pleural fluid greater than 300 mg/dL or a Chow gradient greater than 50 mg/dL is diagnostic of PD -associated hydrothorax (6). The Chow gradient in this patient was calculated to be 534 mg/dL.

**Table 1.** Simultaneous laboratory results of pleural fluid and serum sample.

| | Serum | Pleural fluid |
|---|---|---|
| Serum glucose (mg/dL) | 131 | 665 |
| Lactate dehydrogenase (U/L) | 232 | 5 |
| Total protein (g/dL) | 6.92 | 1.06 |
| Albumin (g/dL) | 3.96 | 0.05 |

Treatment of this complication should be planned according to the patient's clinical condition and preferences. In cases of congenital diaphragmatic defects, pleurodesis may yield positive results. On the other hand, in cases where increased intraperitoneal pressure is considered a priority, PD can be temporarily discontinued and then resumed with minor volume changes (7). This was also the primary planned approach in our case. It was assumed that pleuro-peritoneal leakage could be stopped after the constipation was relieved. However, the hemodialysis program was initiated because the patient did not want to continue PD.

## CONCLUSION

Hydrothorax may develop at relatively late stages in PD patients, although rarely. While obvious congenital defects cause symptoms immediately after the onset of PD, some clinical factors may contribute to development at later stages. Awareness among clinicians will contribute to the correct diagnosis and management of such cases

## DECLARATIONS

**Acknowledgment:** Not applicable
**Ethics Committee Approval Number:** Not necessary
**Informed Consent:** Not necessary
**Referee Evaluation Process:** Externally peer-reviewed
**Conflict of Interest Statement:** Authors declare no conflict of interest.

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