ORIGINAL ARTICLE

# Hepatocyte growth factor as a long-term predictor for total and cardiovascular mortality in patients on peritoneal dialysis

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**KEY WORDS**

cardiovascular mortality, hepatocyte growth factor, peritoneal dialysis, total mortality

**ABSTRACT**

**INTRODUCTION** Hepatocyte growth factor (HGF) is a regenerative protein involved in tissue protection and endothelial repair in response to injury.

**OBJECTIVES** The aim of the study was to assess the effect of increased HGF levels on total and cardiovascular (CV) mortality in patients on peritoneal dialysis (PD) during 6-year follow-up.

**PATIENTS AND METHODS** The study included 55 patients (mean age, 53 years; median duration of PD, 24 months). The ejection fraction (EF) and calcium score (CaSc) were measured. White blood cell (WBC) count and albumin, calcium (Ca), phosphorus (Pi), intact parathormone (iPTH), and high-sensitivity C-reactive protein (hsCRP) levels were measured. Serum levels of HGF, interleukin (IL) 6, and IL-18 were determined using enzyme-linked immunosorbent assays.

**RESULTS** Of all patients, 45% died within 6 years, including 80% from CV complications. HGF significantly correlated with the total (hazard ratio [HR], 1.97; $P = 0.03$) and CV (HR, 2.04; $P = 0.04$) mortality in a univariate Cox regression model. This was confirmed by a multiple model including age, dialysis duration, residual renal function (RRF), albumin, Ca × Pi, EF, and CaSc (HR, 2.24; $P = 0.02$ and HR, 2.58; $P = 0.02$ for total and CV mortality, respectively). Factors negatively affecting patients' survival included WBC count, hsCRP, IL-6, and CaSc, while higher albumin levels and EF were associated with longer overall survival. HGF positively correlated with WBC count ($r = 0.30$, $P = 0.01$), hsCRP ($r = 0.25$, $P = 0.04$), IL-6 ($r = 0.46$, $P = 0.0004$), CaSc ($r = 0.29$, $P = 0.03$), and mean arterial pressure ($r = 0.25$; $P = 0.04$) and negatively with RRF ($r = –0.31$, $P = 0.02$).

**CONCLUSIONS** Increased concentrations of proinflammatory cytokines and an association between HGF levels and CaSc may indicate higher total and CV mortality in patients on PD.

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**INTRODUCTION** Hepatocyte growth factor (HGF) is a mesenchyme-derived pleiotropic protein, which regulates cell growth, motility, morphogenesis, and antiapoptotic activities of various cell types. HGF is also an angiogenic growth factor secreted by the vascular endothelial and smooth muscle cells. The HGF receptor is a protein encoded by the protooncogene, c-met, which is an integral structure of the cytoplasmic membrane epithelial cells and vascular endothelium. HGF is synthesized in large amounts in the liver and secreted into the blood. HGF and its specific receptor, c-met, were found in many localizations such as the brain, heart, kidney, and lung.[1,2] Yang et al.[3] evaluated the effects of intracoronary administration of an adenovirus vector encoding the human HGF (AdHGF) in patients with cardiovascular disease (CVD). One group of patients received both a stent and AdHGF and the other group stent alone. Intracoronary administration of AdHGF resulted in high levels of HGF as well as its c-met receptor, monocyte chemottractant

**TABLE 1** Characteristics of the study group (n = 55)

| Variable | Mean values[a] | Minimum–maximum | Reference values |
|---|---|---|---|
| age, y | 53 ±13 | 19–75 | – |
| sex, men/women, n (%) | 30 (55)/25 (45) | – | – |
| dialysis duration at baseline, mo | 24 (15–51) | 4–100 | – |
| RRF, ml/min/1.73 $m^2$ | 2.22 (1.93–2.63) | 1.34–5.26 | – |
| weekly Kt/V | 1.72 (0.04–4.62) | 0–11.33 | >1.7 |
| WCrCl, l/wk/1.73 $m^2$ | 68.0 (58.8–95.7) | 43.2–213.8 | >45.0 |
| BMI, kg/$m^2$ | 25.3 ±4.1 | 17.2–34.2 | 20–25 |
| SBP, mmHg | 149 ±18 | 105–180 | <130 |
| DBP, mmHg | 90 ±12 | 60–115 | <80 |
| MAP, mmHg | 110 ±11 | 87–133 | 75–100 |
| hemoglobin, g/dl | 11.9 ±1.6 | 7.7–15.3 | 12.0–17.0 |
| total WBC count, × $10^3$/µl | 7.48 ±2.43 | 2.77–14.33 | 4.0–10.0 |
| albumin, g/l | 37.89 ±4.90 | 20.00–47.00 | 35–50 |
| iPTH, pg/ml | 406 (196–806) | 3–2474 | 12–72 |
| Ca, mmol/l | 2.29 ±0.22 | 1.59–2.68 | 2.1–2.4 |
| Pi, mmol/l | 1.76 ±0.50 | 0.79–2.90 | 1.1–1.8 |
| Ca × Pi, $mmol^2/l^2$ | 4.03 ±1.30 | 1.81–7.77 | <4.4 |
| hsCRP, mg/l | 4.18 (1.21–11.40) | 0.16–80.40 | 0.16 – 3.30 |
| HGF, ng/ml | 1.47 (1.05–1.88) | 0.64–3.79 | 0.67–1.99[b] |
| IL-18, pg/ml | 511.0 (378.0–631.0) | 143.0–1619.0 | 37.0–215 |
| IL-6, pg/ml | 7.60 (3.90–17.30) | 0–101.70 | 3.13–12.5[b] |
| EF, % | 64 (60–66) | 30–74 | 55–70 |
| LV mass, g | 268 (185–317) | 102–472 | men, 67–162<br>women, 88–224 |
| CaSc, Agatston units | 93.10 (0–1070.70) | 0–4555.50 | 0–100 |

**a** number of patients (percentage) is given for categorical variables; mean ± standard deviation or median (lower–upper quartile) for continuous variables
**b** reference intervals established for the method by the manufacturer

Abbreviations: BMI – body mass index, Ca – calcium, CaSc – calcium score, DBP – diastolic blood pressure, EF – ejection fraction, HGF – hepatocyte growth factor, hsCRP – high-sensitivity C-reactive protein, IL-6 – interleukin 6, IL-18 – interleukin 18, LV – left ventricular mass, MAP – mean arterial pressure, iPTH – intact parathormone, Pi – phosphorus, RRF – residual renal function, SBP – systolic blood pressure, WBC – white blood cell, WCrCl – weekly creatinine clearance

protein-1 (MCP-1), and interleukin (IL) 10 compared with the control group. Banquet et al.[4] observed that fibroblast growth factor (FGF) and HGF synergistically stimulate vascular cell migration and proliferation in an in-vitro model, and the use of both growth factors in combination results in a more potent and durable angiogenic response than the use of either of the growth factors alone. In a rat model with chronic heart failure, intramyocardial slow release of FGF with HGF stimulates angio- and arteriogenesis and prevents cardiac hypertrophy and fibrosis confirmed by magnetic resonance imaging. Additionally, echocardiography showed improved left ventricular function. HGF is a regenerative factor produced in response to injury and is involved in tissue protection and repair in the endothelium and various organ systems. The serum concentration of this protein is markedly increased in patients with chronic kidney disease (CKD).[5,6] On the other hand, in these patients, a decrease in circulating endothelial progenitor cells may impair vascular regenerative potential and thus contribute to a higher cardiovascular (CV) risk.[7] By promoting angiogenesis and inhibiting apoptosis, endogenous HGF could play an important role in the regeneration of cardiomyocytes after myocardial infarction (MI). HGF is closely associated with hypertension, atherosclerosis, and heart failure. This cytokine enhances kidney regeneration and suppresses the progression of hypertension. An increase in the serum concentration of HGF in the early phase of MI and heart failure may be a significant prognostic marker of CVD.[6,8,9]

Circulating HGF levels are elevated in patients with peripheral arterial disease, MI, CKD (mainly glomerulonephritis), and the presence of calcification.[1,10] HGF gene therapy may affect the regulation of cytokines in patients with CVD and CKD.

The aim of the study was to assess the effect of increased HGF levels on total and CV mortality in a population of patients on peritoneal dialysis (PD) during 6-year follow-up.

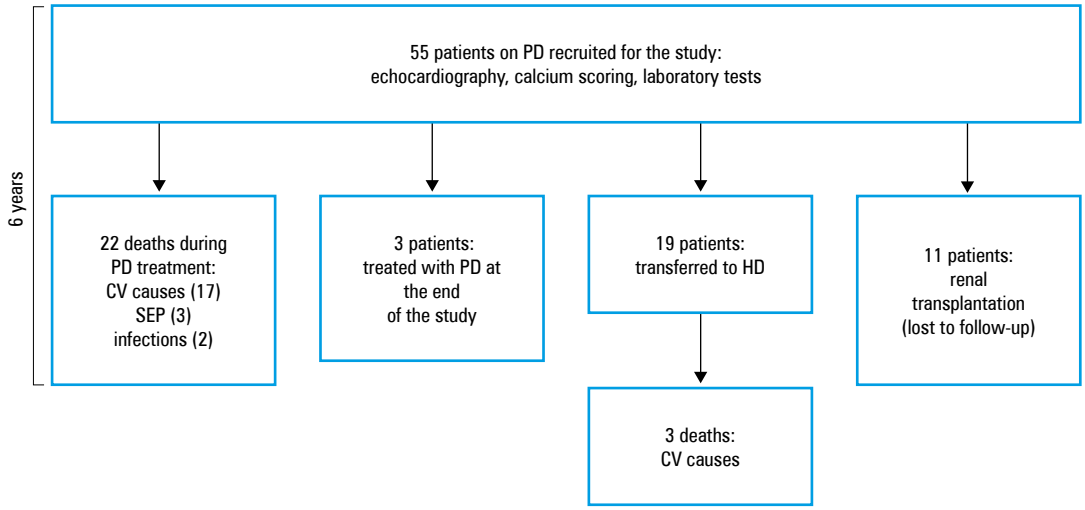


**FIGURE 1** Course of the study
Abbreviations: CV – cardiovascular, HD – hemodialysis, PD – peritoneal dialysis, SEP – sclerosing encapsulating peritonitis

**PATIENTS AND METHODS** The study included 55 patients on PD (25 women, 30 men; mean age, 53 ±13 years). The median duration of dialysis treatment was 24 months (range, 4–100 months). Twenty-seven patients were treated with automated PD and 28 with continuous ambulatory PD. Echocardiography was performed and calcium score (CaSc) was calculated in all patients at baseline. Blood samples were collected for laboratory tests: complete blood cell count, albumin, calcium (Ca), phosphorus (Pi), intact parathormone (iPTH), high-sensitivity C-reactive protein (hsCRP), HGF, IL-6, and IL-18. Data on mortality were collected over a 6-year period (72 months).

On the day of blood collection, routine laboratory tests were performed including the measurement of peripheral blood cell count, Ca, Pi and iPTH levels, and serum concentration of albumin. Serum hsCRP concentration was determined by an immunonephelometric assay using Nephelometer BNII (Siemens, Healthcare Diagnostics, Germany). Serum samples for other laboratory tests were aliquoted and stored at a temperature below –70°C. The measurements of HGF, IL-6, and IL-18 were performed using enzyme-linked immunosorbent assay (ELISA) kits: IL-6 and HGF (R&D Systems ELISA kits, Minneapollis, United States), while IL-18 with the MBL ELISA kit (Nagoya, Japan). The reference ranges for these tests are given in accordance with the values set by the manufacturers (TABLE 1).

The body mass index (BMI) was calculated using the Quetelet's formula. A PD dose was assessed using the following indices: weekly Kt/V, weekly creatinine clearance, and residual renal function (RRF). The assessment of calcifications in the coronary arteries was performed using the multi-row spiral CT (MSCT) Somaton Plus 4 Volume Zoom, using a calcium scoring program (Siemens Company, Nürnberg, Germany). The Agatston score was used to interpret the results, using CaCs expressed in Hounsfield units (HU). The ejection fraction (EF) and left ventricular (LV) mass were measured with transthoracic echocardiography using the Simpson's biplane method (Vivid 7 GE Healthcare, Norway). The mean arterial pressure (MAP) was calculated from the formula: MAP = (systolic blood pressure + 2 × diastolic blood pressure) / 3.

The study was approved by the Bioethics Committee of the Jagiellonian University and all patients signed informed consent to participate in the study.

**Statistical analysis** The number of patients (percentage of the group) was reported for categorical variables and mean ± standard deviation or median (lower–upper quartile) for continuous variables with normal or nonnormal distributions, respectively. The Shapiro–Wilk *W* test was used to assess normality. The Spearman's rank correlation coefficient was calculated to assess correlations. Survival curves were computed using the Kaplan–Meyer method and compared using the log-rank test. The hazard ratios (HR) for total and CV mortality were estimated using univariate and multiple Cox proportional hazard regression models (95% confidence intervals [CI] are reported for each estimate). Deaths occurring after patients' transfer to hemodialysis (HD) were treated as complete observations. All the tests were 2-tailed and the results were considered significant at a *P* value of 0.05 and less. The computations were performed using the Statistica 9.0 software (StatSoft, Inc., United States).

**RESULTS** Of 55 patients, 25 (45%) died within 6 years, including 20 patients (80%) due to CV causes, 3 patients (12%) due to sclerosing encapsulating peritonitis, and 2 patients (8%) due to infections. Twenty-two deaths occurred while patients were treated with PD. During the study, 19 patients (35%) were transferred to HD. In this subgroup, 3 patients died due to CV complications. Eleven patients (20%) were lost to follow-up because they underwent renal transplantation during the study period (FIGURE 1). The lower quartile of the overall survival in the study group was 18 months. The median follow-up period was 60 months (1–72 months; lower–upper quartile, 9–72 months). Baseline clinical characteristics of the patients and the results of biochemical tests

**TABLE 2** Univariate Cox regression models to predict total and cardiovascular mortality

| Independent variable | Total mortality | | Cardiovascular mortality | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| total WBC count, × $10^3$/μl | 1.25 (1.07–1.47) | 0.005 | 1.25 (1.04–1.50) | 0.02 |
| albumin, g/l | 0.88 (0.80–0.97) | 0.009 | 0.94 (0.84–1.06) | 0.3 |
| hsCRP, mg/l | 1.04 (1.01–1.07) | 0.002 | 1.04 (1.01–1.07) | 0.004 |
| IL-6, pg/ml | 1.05 (1.03–1.08) | 0.0002 | 1.05 (1.02–1.09) | 0.0009 |
| HGF, ng/ml | 1.97 (1.09–3.56) | 0.03 | 2.04 (1.03–4.03) | 0.04 |
| EF, % | 0.95 (0.92–0.99) | 0.02 | 0.99 (0.95–1.04) | 0.7 |
| CaSc, 100 Agatston units | 1.04 (1.01–1.06) | 0.01 | 1.05 (1.01–1.08) | 0.002 |

Abbreviations: CI – confidence interval, HR – hazard ratio, others – see TABLE 1

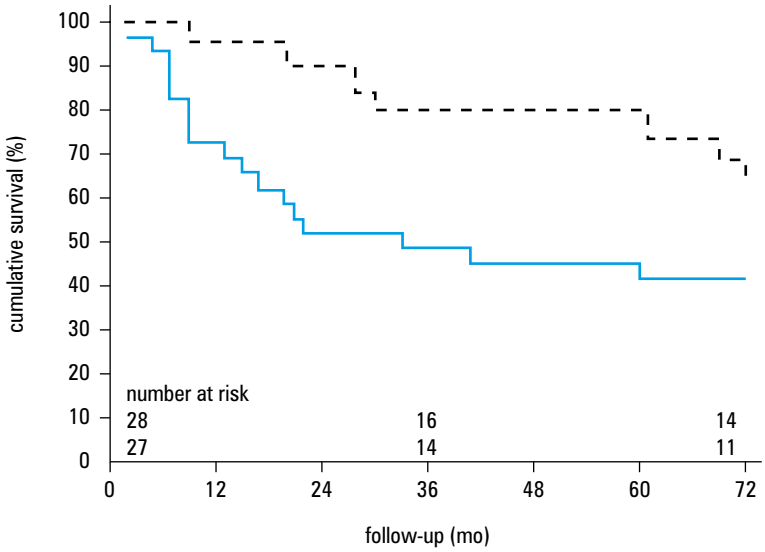


**FIGURE 2** Kaplan–Meier curves showing the overall survival of patients with hepatocyte growth factor (HGF) concentrations below the median value (dashed line) vs. patients with HGF concentrations above or equal to the median value of 1.47 mg/ml (solid line); the survival differs significantly between the groups ($P = 0.04$); numbers at risk in each group at 0, 36, and 72 months are given at the bottom of the graph

as well as EF, LV mass, and CaSc values are presented in TABLE 1.

HGF significantly correlated with total and CV mortality in dialysis patients as shown using univariate Cox regression (TABLE 2). When patients were divided into 2 groups depending on the HGF concentration (below or above the median value of 1.47 ng/ml), the overall survival was significantly lower in the group with higher HGF levels ($P = 0.04$ in the log-rank test) (FIGURE 2). Other factors negatively affecting survival were WBC count, hsCRP, and IL-6 concentrations as well as CaSc. Higher albumin levels and higher EF were associated with longer overall survival in the study group (TABLE 2).

The HGF concentration was significantly positively correlated with inflammatory markers, i.e., WBC count ($r = 0.30$, $P = 0.01$), hsCRP ($r = 0.25$, $P = 0.04$), and IL-6 ($r = 0.46$, $P = 0.0004$). RRF was negatively associated with the HGF level ($r = –0.31$, $P = 0.02$). Moreover, HGF levels were positively correlated with CaSc ($r = 0.29$, $P = 0.03$). HGF correlated with MAP ($r = 0.25$, $P = 0.04$) but not with systolic or diastolic blood pressure. There was no correlation between HGF and LV mass ($r = –0.04$, $P = 0.8$).

In the multiple Cox regression model adjusted for age, dialysis therapy duration, RRF, and Ca × Pi, HGF was shown to be a long-term predictor of total and CV mortality, independent of the albumin concentration, EF, and CaSc (TABLE 3).

**DISCUSSION** To our knowledge, the relationship between HGF level and long-term mortality in CKD patients has not been studied before. Our study showed that the HGF concentration is a long-term predictor of total and CV mortality in CKD patients treated with PD. So far, HGF has been shown to be a strong and independent predictor of mortality in advanced heart failure (especially ischemic). Rychli et al.[11] showed that HGF was associated with increased risk for all-cause mortality. This association was significant after multivariable adjustment for B-type natriuretic peptide (BNP). Patients with high HGF but low levels of BNP had a comparable survival rate to those with elevated BNP but low HGF. Additionally, the dose of angiotensin-converting enzyme inhibitors inversely correlated with HGF concentrations. In another study, Lamblin et al.[12] postulated that HGF and vascular endothelial growth factor may play a role in the pathogenesis of congestive heart failure. This study revealed strong association of HGF with age, diabetes mellitus, and all markers of severity of congestive heart failure. HGF concentrations were higher in patients with a history of a CV event than in those without such history. CV survival rates were as follows: 91% in the first year, 87% in the second year, and 80% after 3 years. The baseline HGF concentration was associated with an increased CV mortality in a multivariable analysis. In patients with CKD, an elevated serum concentration of HGF was associated with concentric left ventricular geometry. Malatino et al.[13] assessed the correlation between HGF and LV geometry in patients on HD. Participants with high HGF had more frequent CV complications. A multivariable analysis showed that this association was independent of other risk factors. In contrast with the above study,[13] we observed no changes in the HGF concentration associated with the difference in the LV mass in our study. Consistent with other reports, the HGF concentration was significantly positively correlated with the markers of inflammation, i.e., CRP and $\alpha_1$-antitrypsin.[14] In

**TABLE 3** Multiple Cox regression models to predict total and cardiovascular mortality

| Independent variable | Total mortality | | Cardiovascular mortality | |
|---|---|---|---|---|
| | HR (95% CI) | *P* value | HR (95% CI) | *P* value |
| dialysis duration, mo | 1.00 (0.99–1.02) | 0.6 | 1.00 (0.97–1.02) | 0.7 |
| age, y | 0.96 (0.91–1.02) | 0.2 | 0.98 (0.93–1.04) | 0.6 |
| RRF, ml/min/1.73 $m^2$ | 1.06 (0.92–1.23) | 0.4 | 1.10 (0.93–1.31) | 0.3 |
| Ca × Pi, $mmol^2/l^2$ | 1.05 (0.69–1.61) | 0.8 | 1.26 (0.76–2.08) | 0.3 |
| albumin, g/l | 0.83 (0.74–0.94) | 0.002 | 0.84 (0.71–0.98) | 0.02 |
| HGF, ng/ml | 2.24 (1.12–4.49) | 0.02 | 2.58 (1.20–5.55) | 0.02 |
| EF, % | 1.01 (0.96–1.05) | 0.2 | 1.02 (0.97–1.08) | 0.3 |
| CaSc, 100 Agatston units | 1.06 (1.03–1.10) | 0.0008 | 1.07 (1.03–1.12) | 0.001 |

Abbreviations: see TABLES 1 and 2

the present study, both HGF and inflammatory markers such as total WBC count, hsCRP, and IL-6 were directly associated with CV mortality and negatively affected patients' survival. These data confirm that subclinical chronic inflammation underlying the development of CVD is an important stimulus for HGF synthesis in dialysis patients. An increase in HGF is likely to represent a component of the protective mechanisms against CV damage. These results are in line with previous studies. Malatino et al.,[6] in a multiple regression model composed of duration of dialysis, age, hemoglobin, immunoglobulin G, and CRP levels showed independent correlations with serum HGF levels. They suggested that increased concentrations of HGF could reflect the extent of the inflammatory response. HD patients had higher HGF levels than patients treated with PD. In the group who underwent color Doppler echocardiography, changes in serum HGF levels correlated independently with the intima–media thickness (IMT). The HGF concentration was elevated in HD patients compared with the healthy population. HGF was significantly correlated with the IMT of the common carotid artery, left ventricular hypertrophy, presence of chronic inflammation, and oxidative stress.[2] In another study, Lee et al.[15] enrolled patients on PD and investigated the relationship between serum levels of proinflammatory cytokines and adipokines. They demonstrated a strong association between HGF and CRP, IL-6, and high-sensitivity tumor necrosis factor α (TNF-α) but not with IL-10 or IL-18. Changes in HGF concentrations were associated with proinflammatory cytokines but not adipokines. The presence of RRF, peritoneal properties, and dialysis glucose load affected the levels of cytokines. Moreover, serum HGF levels in patients on PD depend on the degree of peritoneal damage in the course of PD. Yu et al.[16] demonstrated that peritoneal mesothelial cells (PMC) constitutively synthesized HGF. Lai et al.[17] showed that PMC produced HGF and inflammatory cytokines such as TNF-α, IL-6, and IL-8. Peritoneal macrophages and adipocytes also synthesized IL-6 and peritoneal fibroblasts and macrophages, which stimulated IL-8 and macrophage migration inhibitory factor (MIF). TNF-α and IL-6 are proinflammatory cytokines; MIF and IL-8 are chemotactic factors. By contrast, HGF ameliorates the epithelial–mesenchymal transition induced by high glucose in the peritoneal mesothelium.

In the present study, we showed that in the population of PD patients, HGF predicted both total and CV mortality independently of the EF, CaSc, albumin level, age, and dialysis duration. The levels of HGF positively correlated with CaSc. Coronary calcification is a marker of atherosclerosis and evaluation of the CaSc by MSCT has been recognized as a useful strategy to initiate or intensify treatment to slow atherosclerotic progression. This noninvasive test used to assess CVD in patients with CKD allows to identify coronary artery disease and evaluate the risk of CV events and death. The CaSc identifies calcified plaques using scatter of X-rays and it could be used as a marker of atherosclerosis that might improve the current risk assessment when added to traditional risk factors.[18-20]

In conclusion, our study showed that increased HGF levels in response to vascular damage in dialysis patients correlate with vascular calcifications and predict long-term mortality. Given the relationship between HGF levels and CaSc, increased concentrations of early inflammatory factors such as IL-6, hsCRP, and HGF could be considered as risk factors for total and CV mortality in dialysis patients. Monitoring the levels of HGF may be useful in predicting overall and CV mortality in this patient group.

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ARTYKUŁ ORYGINALNY

# Czynnik wzrostu hepatocytów jako długoterminowy wskaźnik predykcyjny śmiertelności ogólnej oraz z przyczyn sercowo-naczyniowych u chorych dializowanych otrzewnowo

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**SŁOWA KLUCZOWE**

czynnik wzrostu hepatocytów, dializa otrzewnowa, śmiertelność całkowita, śmiertelność sercowo-naczyniowa

**STRESZCZENIE**

**WPROWADZENIE** Czynnik wzrostu hepatocytów (*hepatocyte growth factor* – HGF) jest białkiem naprawczym biorącym udział w ochronie tkanek i naprawie śródbłonka w odpowiedzi na ich uszkodzenie.
**CELE** Celem badania była ocena wpływu podwyższonego stężenia HGF na śmiertelność z przyczyn ogólnych oraz sercowo-naczyniowych (SN) w populacji pacjentów dializowanych otrzewnowo (DO) w okresie 6- letniej obserwacji.
**PACJENCI I METODY** Badaniem objęto 55 pacjentów (średni wiek 53 lata, czas DO – mediana 24 miesiące). Oceniano frakcję wyrzutową lewej komory (*ejection fraction* – EF) oraz stopień uwapnienia tętnic wieńcowych (*calcium score* – CaSc). Oznaczono liczbę leukocytów, stężenie albuminy, wapnia (Ca), fosforanów (Pi), parathormonu (iPTH), białka C-reaktywnego metodą wysokiej czułości (*high-sensititvity C-reactive protein* – CRP). Stężenia HGF, interleukiny 6 i intereukiny 18 w surowicy oznaczono za pomocą testów immunoenzymatycznych.
**WYNIKI** 45% pacjentów zmarło w ciągu 6 lat, w tym 80% z przyczyn SN. Stężenie HGF istotnie korelowało ze śmiertelnością całkowitą (*hazard ratio* [HR] = 1,97; p = 0,03) i SN (HR = 2,04; p = 0,04) w jednokrotnej regresji Coxa. Zależność potwierdzono w modelu wielokrotnym uwzględniającym wiek, czas dializoterapii, resztkową funkcję nerek (RFN), stężenie albuminy, Ca × Pi, EF i CaSc (HR = 2,24; p = 0,02 i HR = 2,58; p = 0,02 odpowiednio dla śmiertelności całkowitej i SN). Negatywnie związane z przeżyciem były również liczba leukocytów, hsCRP i IL-6 oraz CaSc, natomiast większe stężenie albuminy i większa EF wiązały się z dłuższym całkowitym przeżyciem. Stężenie HGF dodatnio korelowało z liczbą leukocytów (r = 0,30; p = 0,01), hsCRP (r = 0,25; p = 0,04), IL-6 (r = 0,46; p = 0,0004), CaSc (r = 0,29; p = 0,03) i średnim ciśnieniem tętniczym (r = 0,25; p = 0,04), zaś ujemnie z RFN (r = –0,31; p = 0,02).
**WNIOSKI** Zwiększone stężenie cytokin prozapalnych oraz zależność między stężeniem HGF a CaSc mogą być wskaźnikiem zwiększonej śmiertelności pacjentów DO z przyczyn ogólnych i SN.

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