Heat shock protein 27 as a predictor of prognosis in patients admitted to hospital with acute COPD exacerbation

Matthias Zimmermann1,2 · Denise Traxler1,3 · Christine Bekos1 · Elisabeth Simader1,4 · Thomas Mueller5 · Alexandra Graf6 · Mitja Lainscak7,8 · Robert Marčun9 · Mitja Košnik9 · Matjaž Fležar9 · Aleš Rozman9 · Peter Korošec9 · Walter Klepetko10 · Bernhard Moser10 · Hendrik J. Ankersmit1,10

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Abstract
Episodes of acute exacerbations are major drivers of hospitalisation and death from COPD. To date, there are no objective biomarkers of disease activity or biomarkers to predict patient outcome. In this study, 211 patients hospitalised for an acute exacerbation of COPD have been included. At the time of admission, routine blood tests have been performed including complete blood count, C-reactive protein, cardiac troponin T and NT-proBNP. Heat shock protein 27 (HSP27) serum concentrations were determined at time of admission, discharge and 180 days after discharge by ELISA. We were able to demonstrate significantly increased HSP27 serum concentrations in COPD patients at time of admission to hospital as compared to HSP27 concentrations obtained 180 days after discharge. In univariable Cox regression analyses, a HSP27 serum concentration $\geq$ 3098 pg/mL determined at admission was a predictor of all-cause mortality at 90 days, 180 days, 1 year and 3 years. In multivariable analyses, an increased HSP27 serum concentration at admission retained its prognostic ability with respect to all-cause mortality for up to 1-year follow-up. However, an increased HSP27 serum concentration at admission was not an independent predictor of long-term all-cause mortality at 3 years. Elevated serum HSP27 concentrations significantly predicted short-term mortality in patients admitted to hospital with acute exacerbation of COPD and could help to improve outcomes by identifying high-risk patients.

Keywords Heat shock protein 27 · Chronic obstructive pulmonary disease · Acute exacerbation · Biomarker · Prognosis · Mortality

Abbreviations
AECOPD Acute exacerbation of chronic obstructive pulmonary disease
CI Confidence interval
COPD Chronic obstructive pulmonary disease
CRP C-reactive protein
ELISA Enzyme linked immunosorbent assay
GOLD Global Initiative For Chronic Obstructive Lung Disease
HR Hazard ratio
HSP Heat shock protein
IQR Interquartile range
LTOT Long-term oxygen therapy
N-terminal pro-brain natriuretic protein

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normal condition (diagnostic), as an indicator of disease can be used to identify individuals with a disease or ab-
health states in individuals or across populations. They characteristics are used in disease detection and monitoring of 
Working Group 2001). In a clinical context, these charac-
teristics are used in disease detection and monitoring of 
Working Group in 1998 (Biomarkers Definitions 
National Institutes of Health Biomarkers Definitions 
Lambers et al. 2009). Increased concentrations of 
2009). 
no proven disease modifying effect (Barnes and Adcock 
bronchodilators or anti-inflammatory corticosteroids, have 
substantial improvement in the understanding of COPD path-
ogenesis over the last years, existing treatments, such as 
bronchodilators or anti-inflammatory corticosteroids, have 
no proven disease modifying effect (Barnes and Adcock 2009).

A blunted regulatory T cell response to tobacco smoking has been identified in COPD patients (Barcelo et al. 2008; 
Lambers et al. 2009). Increased concentrations of 
CD28nullCD8+ cells have been shown (Hodge et al. 2011) 
and lymphocyte senescence seems to be associated with loss 
of molecular chaperone Hsp90 in CD28nullCD8+ T and 
NKT-like cells (Hodge et al. 2016). This loss is associated 
with steroid resistant pro-inflammatory lymphocytes and lung 
function in COPD (Hacker et al. 2009a).

The aim of current therapy is primarily to improve 
aflow, reduce dyspnea and prevent exacerbation 
(Barnes et al. 2003). Episodes of acute exacerbations are 
the major drivers of hospitalisation and death from 
COPD. There are no objective biomarkers of disease ac-
tivity or biomarkers to guide therapeutic choices respec-
tively to risk stratify patients for imminent exacerbations. 
Finding a reliable marker that identifies patients at risk for 
future hospitalisations in order to modify and optimise a 
patient’s current therapy regime may significantly en-
hance prognosis among this group of patients. 
Regrettably, at this stage, there are no clinical tools or 
biomarkers to diagnose COPD exacerbations (Sin et al. 
2015).

Characteristics of an ideal biomarker

A biomarker is a “characteristic that is objectively mea-
sured and evaluated as an indicator of normal biological 
processes, pathogenic processes, or pharmacologic re-
sponses to a therapeutic intervention” as defined by the 
National Institutes of Health Biomarkers Definitions 
Working Group in 1998 (Biomarkers Definitions 
Working Group 2001). In a clinical context, these charac-
teristics are used in disease detection and monitoring of 
health states in individuals or across populations. They 
can be used to identify individuals with a disease or ab-
normal condition (diagnostic), as an indicator of disease 
prognosis (prognostic) or for prediction and monitoring of 
clinical response to an intervention (predictive). Ideally, a 
biomarker should be safe and easy to measure, accurate, 
reproducible across sex and age, modifiable with effective 
therapy, economical and most importantly should enable 
clinicians to better manage their patients (Sin et al. 2015; 
Hollander et al. 2017).

Heat shock proteins in COPD

Although there has been great effort in COPD biomarker 
discovery in recent years, clinical translation and imple-
mentation have not matched these efforts. Possible candi-
dates that have been thoroughly investigated in COPD 
patients are heat shock proteins (HSPs). HSPs belong to 
a highly conserved protein family, which are classified 
according their molecular weight: some are induced in 
response to multiple stressful events to protect the cells 
while others are constitutively expressed. Initially, it was 
believed that HSPs are only present inside the cells. 
Interestingly, several groups recently reported the extra-
cellular presence of HSPs (De Maio and Vazquez 2013). 
Secretion into the extracellular milieu during many path-
ological conditions suggests additional or novel functions 
of HSPs in addition to their intracellular properties. 
Extracellular HSPs are implicated in cell-cell communica-
tion, activation of immune cells, and promoting anti-
flammatory and anti-platelet responses (Reddy et al. 
2018; De et al. 2000).

The heat shock protein 27, which belongs to the group of 
small heat shock proteins, has been studied thoroughly in 
patients with COPD. Increased HSP27 serum concentrations 
in patients with COPD have been reported when compared 
with healthy non-smokers and smokers (Hacker et al. 2009b; 
Unver et al. 2016). Correlation of serum HSP27 concentra-
tions with spirometry analysis and high-resolution computed 
tomography (HR-CT) revealed that HSP27 is an independent 
prognosticator of air trapping and emphysema in a study co-
hort of smokers (Jan Ankersmit et al. 2012). In regard to 
COPD exacerbations, no data on HSP27 serum concentrations 
exist.

The aim of this study was to investigate the role of serum 
HSP27 as a prognostic and predictive marker for all-cause 
mortality in patients hospitalised due to an episode of acute 
exacerbation of COPD (AECOPD) up to 3 years. 
Prognostication of patients with AECOPD could help to im-
prove outcomes by identifying high-risk patients who might 
potentially benefit from intensive inpatient monitoring and 
treatment.

We therefore made a post hoc analysis in patients 
hospitalised due to acute exacerbation, which had been includ-
ed in a controlled clinical trial to assess the effectiveness of 
discharge coordinator intervention compared to care as usual

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The text discusses the role of heat shock proteins, particularly HSP27, in chronic obstructive pulmonary disease (COPD). It highlights the importance of finding reliable biomarkers for disease diagnosis and management, emphasizing the need for safe and easy-to-measure markers that can guide therapeutic choices. The text also mentions the extracellular presence of heat shock proteins and their potential roles in cell-cell communication, immune cell activation, and anti-inflammatory and anti-platelet responses. The study aims to investigate the role of serum HSP27 as a prognostic and predictive marker for all-cause mortality in patients hospitalised due to acute exacerbation of COPD (AECOPD) up to 3 years.
in patients with COPD. Retrospective serum HSP27 measure-
ments were performed at time of hospitalisation, respectively,
at later stages and correlated with survival data. Analytical
performance characteristics have been determined earlier
(Zimmermann et al. 2016).

Materials and methods

Study subjects

The study protocol has been approved by the National
Ethics Committee of the Republic of Slovenia and is reg-
istered at ClinicalTrials.gov (NCT01225627). Informed
and written consent was obtained from each subject
included in the study and all clinical and laboratory tests
were performed in accordance with the Declaration of
Helsinki and the guidelines for Good Clinical Practice of
the Medical University of Vienna. A detailed study
protocol and main findings have been published
previously (Farkas et al. 2011; Lainscak et al. 2013).

From the prospectively enrolled 253 participants, post
hoc analyses were performed with 211 patients due to
missing values or blood samples. All of them were admit-
ted for AECOPD between November 2009 and December
2011 at the University Clinic of Pulmonary and Allergic
Diseases Golnik, Slovenia. Inclusion and exclusion
criteria have been described previously (Farkas et al.
2011). Blood serum samples were collected at admission
to hospital, at time of discharge and 180 days after dis-
charge. At the time of admission, routine laboratory pa-
rameters were determined including complete blood
count, C-reactive protein (CRP), cardiac troponin T
(cTnT) and (N-terminal pro-brain natriuretic peptide
(NT-proBNP). CRP was measured with an
immunoturbidimetric method, cTnT (high sensitivity)
and NT-proBNP using an Electro-Chemiluminescence-
Immunoassay (ECLIA, Elecsys 2010, Roche
Diagnostics). Additionally, serum was obtained after cen-
trifugation of blood samples and aliquots were stored at
−80 °C until further testing.

Endpoint was all-cause mortality. Each patient was follow-
ed for 3 years (i.e., exactly 1095 days after admission to hos-
pital) or until death if occurred earlier. Outcome data were
available for all patients.

Quantification of serum HSP27

In a previously published work (Zimmermann et al. 2014), the
R&D ELISA DuoSet for total HSP27 (DYC1580, R&D
Systems, Minneapolis, MN, USA) showed high diagnostic
accuracy in biochemical diagnosis of lung pathologies, when
compared to other commercially available ELISA Kits. We
therefore used the mentioned ELISA Kit to assess total serum
HSP27 concentrations in one batch analysis according to the
manufacturer’s protocol.

Determination of cutoff values

The cutoff values of HSP27 serum concentrations at admission respectively age for Kaplan-Meier curve analysis and
Cox proportional hazard models for mortality calculations
were determined using Cutoff Finder version 2.1, a freely
available R functions-based web application (Budczies et al.
2012), identifying values with highest diagnostic accuracy.

For cardiac biomarkers, the following cutoff values were
used for survival analysis: age-adjusted values for NTpro-
BNP (ng/L) (Januzzi Jr. et al. 2005) and single values of
14 ng/L for high sensitivity cTnT and 0.5 mg/L for CRP.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics
version 23 (SPSS Inc., Chicago, USA) and GraphPad Prism 6
software (GraphPad Software Inc., LA Jolla, CA, USA) was
used for data visualisation. HSP27 serum concentrations were
compared between different time points using Wilcoxon
signed-rank test. Mann-Whitney U test and Kruskal-Wallis
test were used to compare non-parametric, unpaired variables.
Kaplan-Meier curves and log-rank test were used to evaluate
time to death for different subgroups (HSP27 high/low, NT-
proBNP high/low). Univariable Cox regression models were
performed to identify potential influence factors.
Multivariable Cox proportional hazard models were then used
to further evaluate the prognostic ability of factors being sig-
nificant in the univariable analysis. Results are expressed as
hazard ratio (HR) with corresponding 95% confidence inter-
vals (CI). P values were corrected for multiple testing.

Dunn correction was used for post hoc tests in multiple
group comparison. All tests were performed in a two-sided
manner. Data are presented as median ± interquartile range
(ICR). P values equal or below 0.05 were considered as sta-
tistically significant.

Results

Study population

A total of 211 patients were included. Baseline characteristics
are summarised in Table 1. They were predominantly males
(71%) with advanced COPD (GOLD II-IV) and various co-
morbidities. All patients received COPD specific therapy ac-
cording to guidelines. Median age was 72 (IQR, 64–77) years.
Follow-up time was 1095 days. The number of deaths at

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90 days after discharge was 14 (6.5%), 26 at 180 days (12.0%), 40 after 1 year (18.4%) and 95 after 3 years (43.8%). For survival analysis, cutoff values with highest diagnostic accuracy at time of admission have been identified using a cutoff finder (HSP27 ≥3098 pg/ml respectively age 72 years). Patients who had HSP27 concentrations above the defined cutoff were significantly older, kidney function was decreased and CRP and NT-proBNP concentrations were increased (Table 1).

### HSP27 in COPD patients

Systemic HSP27 concentrations in healthy control patients were assessed in a previous study. Median HSP27 concentration was 1482 pg/ml (IQR 1136–2071 pg/ml) in healthy non-smokers (Zimmermann et al. 2012).

Median HSP27 concentrations in our patient cohort was 2227 (IQR, 1560–3070) pg/ml at admission (211 patients), 2037 (IQR, 1504–2836) pg/ml at discharge (295 patients) and 1636 (IQR, 1333–2405) pg/ml at 180 days after discharge (113 patients). HSP27 concentrations at admission were significantly increased compared to 180 days after discharge (Table 1, p = 0.02).

HSP27 concentration at all time points was not significantly associated with GOLD classification. However, HSP27 concentrations correlated significantly with age at admission (r = 0.329, p < 0.001) and discharge (r = 0.244, p = 0.001), but not 180 days after discharge (r = 0.173, p = 0.066).

| Table 1 Patient characteristics (N = 211). Data are presented as median ± interquartile range (IQR) or number (%). HSP27 data are presented as median ± interquartile range (IQR) |
|-----------------------------------|-----------------|-----------------|----------------|-----------------|-------------------|
| All patients                      | HSP27 high ≥3098 pg/mL | HSP27 low <3098 pg/mL | p value | Survivors at 3 years | Decedents at 3 years | p value |
|-------|-----------------|-----------------|----------------|-----------------|-------------------|-----------------|
| Number | 211             | 51              | 160           | 115             | 96                |                  |
| Age (median ± IQR) | 72 (64–77) | 76 (62–76) | 115 (72%–45% (28%) | <0.001 | 69 (61–76) | 74 (69–80) | <0.001 |
| Gender (male/female) | 150 (71%)/61 (29%) | 35 (69%)/16 (31%) | <0.001 | 74 (64%)/41 (36%) | 76 (79%)/20 (21%) | <0.022 |
| GOLD class | | | | | | |
| GOLD 2 | 25 (12%) | 22 (14%) | 19 (17%) | 6 (6%) |                  |                  |
| GOLD 3 | 95 (45%) | 67 (42%) | 55 (48%) | 40 (42%) |                  |                  |
| GOLD 4 | 91 (43%) | 71 (44%) | 41 (36%) | 50 (52%) |                  |                  |
| LTOT | 47 (22%) | 37 (23%) | 19 (17%) | 28 (29%) |                  |                  |
| Concomitant diseases | | | | | | |
| Heart failure | 56 (27%) | 39 (23%) | 25 (22%) | 31 (32%) | <0.001 | 0.088 |
| Arterial hypertension | 51 (43%) | 38 (42%) | 25 (40%) | 26 (46%) | <0.001 | 0.578 |
| Ischemic heart disease | 17 (14%) | 14 (15%) | 7 (8%) | 9 (16%) | <0.001 | 0.794 |
| Arterial fibrillation | 19 (16%) | 13 (14%) | 7 (11%) | 12 (21%) | <0.001 | 0.209 |
| Diabetes mellitus | 27 (23%) | 22 (24%) | 12 (19%) | 15 (27%) | <0.001 | 0.385 |
| BMI (kg/m², median ± IQR) | 25.7 (23.2–30.4) | 26.0 (23.7–30.7) | <0.001 | 25.4 (23.5–30.1) | 26.5 (229–309) | <0.049 |
| Tiffenau index (% median ± IQR) | 41 (32–52) | 40 (31–51) | <0.001 | 41 (33–51) | 41 (30–54) | <0.804 |
| CRP (mg/L, median ± IQR) | 23.9 (4.2–75.6) | 18.4 (3.3–544) | <0.001 | 189 (34–749) | 28.7 (7.2–76.4) | <0.334 |
| cTnT (ng/L, median ± IQR) | 0.00 (0.0–18.0) | 0.00 (0.0–9.5) | <0.001 | 0.00 (0.0–11.0) | 0.00 (0.0–25.5) | <0.011 |
| NT-proBNP (ng/L, median ± IQR) | 471.2 (129.7–692.0) | 308.6 (117.7–197.5) | <0.001 | 2079 (892–945.1) | 101.8 (324.5–2527.0) | <0.001 |
| eGFR (CKD-EPI) (ml/min/1.73 m², median ± IQR) | 81.0 (64.0–92.0) | 84.0 (70.0–94.0) | <0.001 | 81.0 (65.0–92.0) | 805 (630–920) | <0.835 |
| HSP27—admission (pg/ml, median ± IQR) | 2227 (1560–3070) | 1931 (1425–2384) | <0.001 | 2205 (1481–2802) | 227 (1713–2317) | <0.225 |
| HSP27—discharge (pg/ml, median ± IQR) | 2037 (1504–2836) | 1857 (1419–2521) | <0.001 | 2002 (1496–2836) | 216 (150–2783) | <0.961 |
| HSP27—180 days (pg/ml, median ± IQR) | 1636 (1333–2405) | 1580 (1305–2130) | <0.001 | 1643 (1355–2418) | 1621 (1332–1972) | <0.705 |
Survival analysis

Outcome analysis using Kaplan-Meier survival curves are presented in Fig. 1. Patients with HSP27 concentrations above the cutoff showed a significantly increased risk of death ($p = 0.02$). The median survival time for patients with values above the cutoff was 838 [CI 95% 153–1095] as compared to 1095 [CI 95% 626–1095] days ($p = 0.007$).

Potential risk factors for mortality were selected by univariable analyses. HSP27 demonstrates a significant predictive ability for short- and long-term mortality in the univariable analyses (Table 2, 3 year: HR 1.7, CI 95% 1.1–2.6, $p = 0.021$).

Variables that were significant in univariable analysis, such as age, gender, GOLD class, cTnT, and NT-proBNP, were included as adjusting covariates in multivariate analysis to identify potential factors for prediction of mortality. In multivariate Cox proportional hazard regression analysis, age, GOLD class and NT-proBNP were significantly associated with an increased 3 year mortality (Table 3, Fig. 2). However, HSP27 did not remain significant in the model (using backward selection) for 3-year mortality, but it remained significant for short-term outcomes (Table 3, Fig. 2). A significant increased risk of death for patients with higher HSP27 values was found for 90 days (HR, 4.4; 95% CI, 1.5–12.8), 180 days (HR, 4.3; 95% CI, 2.0–9.4) and 1 year (HR, 2.4; 95% CI, 1.3–4.7) after discharge.

The combination of HSP27 and NT-proBNP in a Kaplan-Meier survival analysis showed a higher survival in the NT-proBNP-low/HSP27-low group when compared with NT-proBNP-low/HSP27-high after 2 years (log-rank test = 5.373, $p = 0.02$).

Association with other markers

Elevated NT-proBNP and cTnT concentrations at admission were significantly associated with fatal outcome over the follow-up period (Fig. 1). Adjusted Cox proportional hazard models were built using cardiac biomarkers (Table 3). As CRP,
cTnT and NT-proBNP have already been identified as markers that predict prognosis in COPD patients after an episode of acute exacerbation (Marcun et al. 2012; Brekke et al. 2008; Hoiseth et al. 2011; Medina et al. 2011; Chang et al. 2011), we have correlated HSP27 concentrations with those markers. At admission, serum concentrations of HSP27 correlated significantly with CRP ($r = 0.240$, $p < 0.001$), cTnT ($r = 0.353$, $p < 0.001$) and NT-proBNP ($r = 0.429$, $p < 0.001$).

Due to its small size, renal elimination of HSP27 is conceivable and we could show a significant association of HSP27 serum concentrations with kidney function. HSP27 correlated with eGFR ($r = -0.375$, $p < 0.001$).

### Discussion

COPD exacerbations can be life threatening and are the major drivers for hospitalisation of COPD patients. Furthermore, they are believed to contribute to permanent lung changes and permanent decrements in lung function.

In the current study, we were able to demonstrate significantly increased serum HSP27 concentrations in COPD patients at time of admission to hospital due to an episode of acute exacerbation and a decrease of these concentrations after decline of acute symptoms and discharge from hospital. Furthermore, we identified a HSP27

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**Table 2** Univariable Cox proportional hazards analysis for prognostic factor of outcome

| Factor                  | All-cause mortality at 90 days | All-cause mortality at 180 days | All-cause mortality at 1a | All-cause mortality at 3a |
|-------------------------|--------------------------------|--------------------------------|--------------------------|--------------------------|
|                         | HR (CI)                        | HR (CI)                        | HR (CI)                  | HR (CI)                  |
| Age ($\geq 72\text{a}$) | 1.3 (0.5–3.7) n.s.              | 2.2 (1.0–5.1) n.s.              | 2.7 (1.3–5.4) 0.003      | 1.9 (1.3–2.9) 0.001      |
| Gender (male)           | 0.7 (0.2–2.4) n.s.              | 0.9 (0.4–2.1) n.s.              | 0.9 (0.5–1.9) n.s.       | 0.6 (0.4–1.0) 0.043      |
| GOLD (I, II, III)       | 2.0 (0.8–4.9) n.s.              | 2.3 (1.2–4.7) 0.017             | 1.8 (1.1–3.0) 0.024      | 1.6 (1.2–2.2) 0.002      |
| CRP ($\geq 0.5 \text{mg/L}$) | 4.5 (0.6–35) n.s.            | 2.7 (0.8–9.1) n.s.              | 1.6 (0.7–3.6) n.s.       | 1.4 (0.9–2.3) n.s.       |
| cTnT ($\geq 14 \text{ng/L}$) | 1.0 (0.3–3.1) n.s.            | 1.6 (0.7–3.5) n.s.              | 2.1 (1.1–4.0) 0.017      | 1.6 (1.0–2.4) 0.029      |
| NT-proBNP (age-adjusted) | 1.7 (0.6–4.7) n.s.              | 2.3 (1.1–5.1) 0.032             | 3.3 (1.7–6.4) < 0.001    | 2.4 (1.6–3.6) < 0.001    |
| HSP27 ($\geq 3098 \text{pg/ml}$) | 4.4 (1.5–12.8) 0.006         | 4.1 (1.9–8.9) < 0.001           | 3.1 (1.7–5.7) < 0.001    | 1.7 (1.1–2.6) 0.021      |

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**Fig. 2** Hazard ratios (HR) and 95% confidence interval (CI) in univariable (grey bar) and multivariable (red bar) Cox regression analysis after 90 days (a), 180 days (b), 1 year (c) and 3 years (d). Variables remaining in the model after multivariable analyses are presented in red.
serum cutoff value serving as significant predictor for both short- and long-term mortality using Kaplan-Meier curve analyses and univariate Cox proportional hazard models. We were able to confirm previous findings that NT-proBNP and cTnT predict outcome of these patients.

After adjusting the model for other markers that are known to be associated with mortality in COPD, only HSP27 retained its prognostic performance for short-term mortality.

However, we were not able to significantly correlate serum HSP27 in patients with manifest COPD exacerbation and previous COPD staging according to the GOLD classification (Hacker et al. 2009b).

Although there have been great advances in the understanding of COPD pathogenesis over the last years, biomarker discovery and implementation into the realm of clinics remains challenging. By now, most biomarkers failed to make it beyond the discovery stage. This may be due to the heterogeneity of disease pathogenesis. COPD is not a single entity; airflow limitation is caused by highly variable molecular processes (Lange et al. 2015).

If there is a benefit in serum HSP27 detection in COPD patients still remains unclear. Although HSP27 showed statistical trends to serve as a biomarker in previous works, the diagnostic role remains a matter of debate, as several other conditions and comorbidities may affect serum concentrations. Increased concentrations of circulating HSP27 are reported in different cancers, including lung cancer (Zimmermann et al. 2012), breast cancer (Fanelli et al. 1998; Banerjee et al. 2011), hepatocellular carcinoma (Gruden et al. 2013), pancreatic carcinoma (Liao et al. 2009; Melle et al. 2007), gastric adenocarcinoma (Huang et al. 2010), endometrial cancer and leukemia. Lastly, elevated concentrations of circulating HSP27 have been observed in patients with cardiovascular disease (Jozefowicz-Okonkwo et al. 2009; Park et al. 2006; Zhang et al. 2017; Jin et al. 2014; Heidari-Bakavoli et al. 2012), multiple sclerosis (Ce et al. 2011), diabetes (Gruden et al. 2008; Jakhotia et al. 2018) or renal injury (Jakhotia et al. 2018; Musial and Zwolinska 2012; Lebherz-Eichinger et al. 2012). All these observations culminate to suggest that HSP27, when found its way to the extracellular milieu, seems to have manifold functions, similar as reported from its intracellular presence. Secreted HSP27 plays an instrumental role in cell-to-cell communication, signalling, immunity and inflammation (Reddy et al. 2017).

Despite lacking disease specificity, current observations suggest that HSP27 concentrations can predict disease progress and short-term mortality after COPD exacerbation. Prognostication with HSP27 determination could help to improve outcomes by identifying high-risk patients who might potentially benefit from intensive monitoring and early referral for advanced therapies. It could therefore be a useful tool for clinical decision-making at time of admission.

### Conclusions

Can HSP27 concentrations be used as a predictive and prognostic marker in COPD patients? To obtain a satisfactory answer to this question, further data on a larger population are needed. Results from this initial discovery experiment should be replicated in other cohorts to ensure stability and generalisability of data. More prospective clinical trials are needed to establish optimal cutoff values for survival predictions.

The major limitation of the current study is the fact, that no intervention apart from standard care treatment was performed. So one can only hypothesise that HSP27 serum concentrations can guide therapeutic decisions and enable clinicians to better manage their patients with AECOPD. Furthermore, serum concentrations of HSP27 in healthy individuals may be affected by large intra-individual variation, and assays to date have lacked appropriate standardisation (Zimmermann et al. 2016).

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