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A history of diabetes but not hyperglycaemia during exacerbation of obstructive lung disease has impact on long-term mortality: a prospective, observational cohort study

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ABSTRACT

Objective: Hyperglycaemia is very common during exacerbations of asthma and chronic obstructive pulmonary disease (COPD). However, its clinical significance is not clear. The objective of the present study was to assess whether exacerbation-associated hyperglycaemia affects long-term mortality in these patients.

Design: A prospective, observational cohort study.

Setting: A single hospital in eastern Finland.

Participants: 153 consecutive patients who were hospitalised due to mild to moderate obstructive lung disease exacerbation (110 with asthma and 43 with COPD) and who survived at least 30 days.

Interventions: Plasma glucose levels were recorded seven times during the first day on the ward. Several possible confounders were also recorded. The median follow-up time was 6 years and 2 months.

Results: During the follow-up, 57 (37%) of the patients died. Previously diagnosed diabetes was strongly associated with elevated mortality (adjusted HR (aHR) 3.03 (1.28 to 7.18). The highest fasting glucose value (aHR 1.10 (1.01 to 1.20) per 1 mmol/L) and the highest postprandial glucose value ((aHR 1.07 (1.00 to 1.16)) were also associated with late mortality. However, the associations between highest glucose values and mortality vanished when the diagnosis of diabetes was included in the same model. Within the patients without diabetes, neither fasting (aHR 0.92 (0.42 to 2.02)) nor postprandial ((aHR 1.04 (0.50 to 2.12)) hyperglycaemia was associated with late mortality. There were no statistically significant differences in the underlying causes of death between the patients with and without diabetes.

Conclusion: A history of diabetes but not hyperglycaemia during exacerbation of obstructive lung disease has impact on long-term mortality.

Strengths and limitations of this study

- Plasma glucose levels were carefully measured during the exacerbations with seven plasma glucose measurements during the first day on ward.
- The prospective nature of the study provided comprehensive collection of information about possible confounders.
- The main limitation of the present study is the relatively small number of patients.
- The present population consists of patients with mild to moderate exacerbations. Therefore, the results cannot be generalised to all hospitalised patients with asthma or chronic obstructive pulmonary disease exacerbations.

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showed that as many as 79% of patients without diabetes showed either fasting or postprandial hyperglycaemia during the exacerbation.[1] Almost all (96%) of the patients with diabetes were hyperglycaemic during the exacerbation.

There are several possible causes for hyperglycaemia during acute exacerbations of obstructive lung diseases. First, standard treatment of the exacerbations includes β-2-adrenergic bronchodilators and oral glucocorticoids, both potent inducers of hyperglycaemia.[2–4] Second, hyperglycaemia may reflect the severity of the exacerbation, since stress is a well-known trigger of hyperglycaemia.[5] Third, pre-exacerbation health status probably also affects glucose levels.[6]

At the moment, the relative contributions of these causes are unknown. If the first cause is dominant, hyperglycaemia during exacerbation would probably not relate to the patients' long-term prognosis. On the contrary, the last two explanations might indicate a poor prognosis. One study has

INTRODUCTION

Hyperglycaemia is common during acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD). A recent study

suggested that hyperglycaemia during COPD exacerbation is related to high in-hospital mortality.[7] The impact of exacerbation-associated hyperglycaemia on late mortality has not been investigated but it is known that diabetes is associated with high late mortality after COPD exacerbation.[8 9] These associations are complicated by the diabetes medication since the common diabetes drug metformin has been reported to offer survival benefit among patients with diabetes and COPD.[10] The primary purpose of the present study was to investigate whether exacerbation-associated hyperglycaemia affects late mortality in patients with either asthma or COPD. The secondary purposes were to investigate the relations of diabetes and metformin medication to late mortality.

METHODS
Study design and the population
This prospective, observational cohort study was carried out at Kuopio University Hospital in Finland. From November 2006 to May 2008 all adult patients admitted to the pulmonology ward due to acute exacerbation of asthma or COPD were recruited. Patients were not included if they had severe disease requiring treatment in the intensive or intermediate care unit. During that time, 186 patients were admitted (figure 1). Of them, 32 were excluded: 13 patients could not give their informed consent due to confusion, 10 patients were missed due to technical reasons, 6 refused to participate and 3 patients were missed due to diverse reasons. One of the 154 included patients died within 30 days after admission (early death) and was not included in the analysis. At discharge, the attending physician was asked whether the patient suffered mainly from asthma or COPD. Among the 153 patients in the final analysis, 110 (72%) suffered from probable asthma and 43 (28%) from probable COPD. The proportion of ever-smokers was 49% among the patients with asthma and 95% among the patients with COPD. The baseline results have been
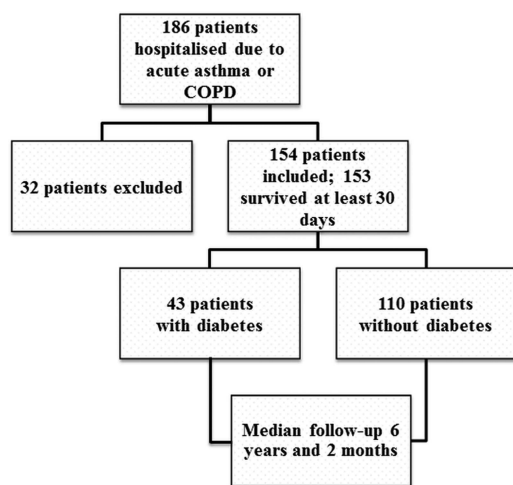
published before.[1] All patients gave their written informed consent.

Measurements during exacerbation
During the first 24 h on the ward, plasma glucose was determined seven times, at 3:00, before breakfast, before lunch, after lunch, before dinner, after dinner and at bedtime. In addition, family history for diabetes and pre-pneumonia Karnofsky performance score was assessed. Karnofsky score is a general measure of patient independence and has been utilised most often in patients with cancer.[11 12] At admission, height, weight, waist circumference, oxygen saturation, blood pressure, temperature and heart rate were measured. Blood tests included glycosylated haemoglobin (HbA1c), N-terminal pro-B-type natriuretic peptide (NT-proBNP), C reactive protein, leucocytes, urea and arterial blood gas analysis. Spirometry was not performed.

A detailed description of the methods has been published before.[1] However, the NT-proBNP analysis will be described here for the first time. It was added to the present study since it has been shown to predict acute[13] and 6-month[14] mortality in COPD exacerbations. NT-proBNP was measured from the blood sample collected at admission utilising a commercially available electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany).

Medication during exacerbation
All patients were treated with oral prednisolone tablets and inhaled salbutamol with doses chosen by the attending physician. Salbutamol was administered via a metered dose inhaler and a spacer device in 142 cases and via nebuliser in 11 cases. Antibiotics were prescribed when the attending physician considered them necessary. The previous metformin medication was suspended during hospitalisation but continued at discharge. A detailed description of the medications has been published before.[1]

Definitions
A doctor's diagnosis of diabetes was defined as diabetes that had been diagnosed by a physician before the exacerbation, and verified from patient files. Screening diabetes was defined as presence of admission HbA1c $\geq 6.5\%$ in a patient without a doctor's diagnosis of diabetes.[15] All diabetes indicates the presence of either a doctor's diagnosis of diabetes or screening diabetes. Fasting hyperglycaemia was defined as plasma glucose >6.9 mmol/L detected at 3:00 or at 7:00, before breakfast. Postprandial hyperglycaemia was defined as plasma glucose >11.1 mmol/L detected during the daytime or in the evening.[5] Any hyperglycaemia indicates the presence of either fasting or postprandial hyperglycaemia. Elevated NT-proBNP was defined as plasma concentration above 450 ng/L for patients younger than 50 years, above 900 ng/L for patients aged 50–75 years and above 1800 ng/mL for patients older than 75 years.[16]

Figure 1 Inclusion of patients (COPD, chronic obstructive pulmonary disease).

Follow-up after exacerbation

In September 2013, the survival status was obtained in all patients from the National Statistical Service of Finland. The immediate and underlying causes of death, according to the International Classification of Diseases V.10, were obtained from death certificates. The median follow-up was 6 years and 2 months.

Statistical analysis

Receiver operator curves (ROC) were produced for the continuous variables to define the best cut-off values to predict death during follow-up. However, established cut-off values were used for the plasma glucose and HbA1c values.[5][15] Comparative survival curves were constructed using Kaplan-Meier methodology. The unadjusted HRs were assessed utilising univariate Cox regression analysis. The assumption of proportional hazard was checked by graphically comparing the hazard curves. To determine the adjusted HRs (aHR) for the predictor variables, Cox multivariate regression analysis was utilised. In this analysis patients with missing data were excluded. The outcome variable was mortality from 30 days after admission up to the end of follow-up. The predictor variables were highest fasting plasma glucose level during exacerbation, highest postprandial plasma glucose level during exacerbation, doctor's diagnosis of diabetes, screening diabetes and all diabetes. A confounder was a variable that associated both with diabetes or hyperglycaemia, and mortality

Frequency comparison was performed by χ^2 test. Student t test and Pearson correlation coefficient were utilised when appropriate. Categorical data are expressed as percentages and continuous data as means and 95% CIs. Statistical significance was defined as a p value of <0.05. Analyses were performed using SPSS V.19.0 for the personal computer (SPSS, Inc, Chicago, Illinois, USA).

RESULTS

Among the 153 patients, there were 23 patients with a doctor's diagnosis of diabetes, 20 patients with a screening diagnosis of diabetes and 110 patients without any form of diabetes (table 1). Fasting hyperglycaemia was detected in 91%, 90% and 63% of the patients in each group, respectively (p=0.003), and postprandial hyperglycaemia in 83%, 80% and 54%, respectively (p=0.006). Among the patients with a doctor's diagnosis of diabetes, 14 used metformin, 7 used sulfonylureas and 10 used insulin.

Univariate associations with late mortality

Of the predictor variables, only the highest postprandial glucose value showed a suggestive association with late mortality in the total group of 153 patients (table 2). Within the three subgroups divided by the diabetic status, neither the highest fasting nor highest postprandial glucose levels showed a statistically significant association with late mortality in univariate analysis (data not shown). Table 2 includes all baseline variables that showed a statistically significant association with late mortality. There were several other baseline variables that were not associated with mortality and were not included in table 2. For example, elevated NT-proBNP was present in 19 out of the 150 patients (13%) in whom this information was available. It did not associate with late mortality (HR 1.48 (0.72 to 3.01). C reactive protein value was often elevated in this population (mean 62 (48–75) mg/L), but it did not associate with mortality either (HR 1.00 (1.00 to 1.01) per 1 mg/mL).

Multivariate associations with late mortality

The following confounders were included in the multivariate models: age, body mass index (BMI), Karnofsky score, presence of COPD, oxygen saturation and urea (table 3). Among the total group of 153 patients, doctor"s diagnosis of diabetes was strongly associated

Table 1 Baseline characteristics of the patients with doctor's diagnosis of diabetes, patients with screening diabetes and patients without diabetes

	Doctor's diagnosis of diabetes (N=23)	Screening diabetes (N=20)	No diabetes (N=110)	p Value
Age, years	64.4 (59.1 to 69.9)	68.8 (64.8 to 72.8)	64.3 (61.3 to 67.2)	0.43
Male gender	52%	70%	51%	0.29
Family history of diabetes	62%	44%	33%	0.037
Waist circumference (cm)	113 (108 to 119)	104 (99 to 109)	104 (101 to 107)	0.013
BMI (kg/m^2)	34.2 (31.6 to 36.9)	28.8 (25.9 to 31.7)	28.6 (27.3 to 30.0)	0.002
HbA1c (%)	7.53 (6.89 to 8.17)	7.00 (6.65 to 7.36)	5.81 (5.73 to 5.88)	<0.001
Peak fasting glucose value (mmol/L)	12.6 (10.6 to 14.6)	10.5 (8.43 to 12.5)	8.10 (7.72 to 8.47)	<0.001
Peak postprandial glucose value (mmol/L)	17.7 (15.1 to 20.3)	14.0 (11.8 to 16.2)	11.6 (11.2 to 12.1)	<0.001
Presence of COPD	9%	60%	26%	0.001
Ever smoking	52%	90%	59%	0.018
Karnofsky score <90%	48%	65%	44%	0.21
Admission oxygen saturation (%)	94.2 (92.3 to 96.0)	89.3 (86.6 to 92.0)	92.1 (91.0 to 93.2)	0.013
Urea (mmol/L)	7.83 (5.93 to 9.73)	8.12 (5.84 to 10.4)	6.32 (5.69 to 6.95)	0.049

The data are presented either as percentage of patients showing the feature or means (95% CIs).
BMI, body mass index; COPD, chronic obstructive pulmonary disease; HbA1c, glycosylated haemoglobin expressed as percentage of total haemoglobin.

Table 2 The univariate associations of basic characteristics with late mortality in 153 patients with acute asthma or COPD

Characteristic	Percentage of patients with the characteristic	HR (95% CI)	p Value	Missing values
		Association with late mortality		
Age >71 years	40	4.17 (2.39 to 7.29)	<0.001	0
Male gender	54	2.84 (1.59 to 5.06)	<0.001	0
BMI <28.8 kg/m^2	50	2.40 (1.38 to 4.16)	0.002	0
Ever smoking	62	2.76 (1.46 to 5.21)	0.002	0
Karnofsky score <90%	47	2.27 (1.32 to 3.89)	0.003	1
Presence of COPD	28	3.94 (2.33 to 6.67)	<0.001	0
Diastolic blood pressure <79 mm Hg	41	2.72 (1.59 to 4.68)	<0.001	3
Oxygen saturation <93%	42	2.48 (1.43 to 4.30)	0.001	6
Urea >5.75 mmol/L	50	2.43 (1.36 to 4.34)	0.003	14
Duration of hospitalisation >6 days	45	1.84 (1.08 to 3.12)	0.024	1
Doctor's diagnosis of diabetes	15	1.51 (0.77 to 2.95)*	0.23	0
Screening diabetes	13	1.25 (0.58 to 2.68)*	0.57	4
All diabetes	29	1.42 (0.82 to 2.48)*	0.22	4
Fasting hyperglycaemia >6.9 mmol/L	71	1.43 (0.78 to 2.62)	0.24	0
Highest fasting glucose value		1.03 (0.96 to 1.11)†	0.42	0
Postprandial hyperglycaemia >11.1 mmol/L	61	1.48 (0.85 to 2.57)	0.16	0
Highest postprandial glucose value		1.05 (0.99 to 1.11)†	0.092	0

The continuous variables are divided by the best cut-off values, which predict death during follow-up according to ROC curves except the HbA1c and plasma glucose values, which are divided according to international recommendations.[15]
*Compared with patients without any form of diabetes.
†HR is expressed per 1 mmol/L of plasma glucose.
BMI, body mass index; COPD, chronic obstructive pulmonary disease; HbA1c, glycosylated haemoglobin expressed as percentage of total haemoglobin; ROC, receiver operator curve.

with late mortality with an aHR of 3.03 (1.28 to 7.18; figure 2). On the contrary, the screening diabetes did not show any association. The highest fasting and postprandial glucose values were also modestly associated with late mortality. When highest fasting glucose value and doctor's diagnosis of diabetes were both added to the same multivariate model, the latter showed stronger association with mortality (aHR 1.05 (0.95 to 1.17) and aHR 2.59 (0.98 to 6.88), respectively). Furthermore, when highest postprandial glucose value and doctor's diagnosis of diabetes were both added to the same multivariate model, only the latter was statistically significantly associated with mortality (aHR 1.03 (0.95 to 1.12) and aHR 2.81 (1.07 to 7.39), respectively). To investigate whether metformin would offer survival benefit in the

patients with diabetes, doctor's diagnosis of diabetes and metformin were both added to the same multivariate model. In this analysis, use of metformin showed a suggestive association with increased mortality risk (aHR 4.07 (0.84 to 19.7)) while the association between diabetes and mortality vanished (aHR 1.32 (0.30 to 5.88)). Among the 130 patients without doctor's diagnosis of diabetes neither fasting nor postprandial glucose values were associated with late mortality (table 3).

Mortality rates and causes of death
The mortality rate at the end of follow-up was 38 among the 110 patients without diabetes, 11 among the 23 patients with doctor's diagnosis of diabetes and 8 among the 20 patients with screening diagnosis of diabetes. The

Table 3 Adjusted HRs of various glucose metabolism abnormalities for late death after obstructive lung disease exacerbation

	All patients, N=153, aHR (95% CI)	Patients without doctor's diagnosis of diabetes, N=130, aHR (95% CI)
Doctor's diagnosis of diabetes	3.03 (1.28 to 7.18)*	ND
Screening diabetes	0.70 (0.31 to 1.59)*	0.72 (0.30 to 1.67)
All diabetes	1.29 (0.68 to 2.44)*	ND
Fasting hyperglycaemia >6.9 mmol/l	1.09 (0.52 to 2.29)	0.92 (0.42 to 2.02)
Highest fasting glucose value	1.10 (1.01 to 1.20)†	1.10 (0.96 to 1.25)†
Postprandial hyperglycaemia >11.1 mmol/L	1.18 (0.60 to 2.30)	1.04 (0.50 to 2.12)
Highest postprandial glucose value	1.07 (1.00 to 1.16)†	1.05 (0.94 to 1.19)†

In each case, the following confounders were included in the Cox multivariate regression analysis: age, body mass index, Karnofsky score, presence of chronic obstructive pulmonary disease, oxygen saturation and urea.
*Compared with patients without any form of diabetes.
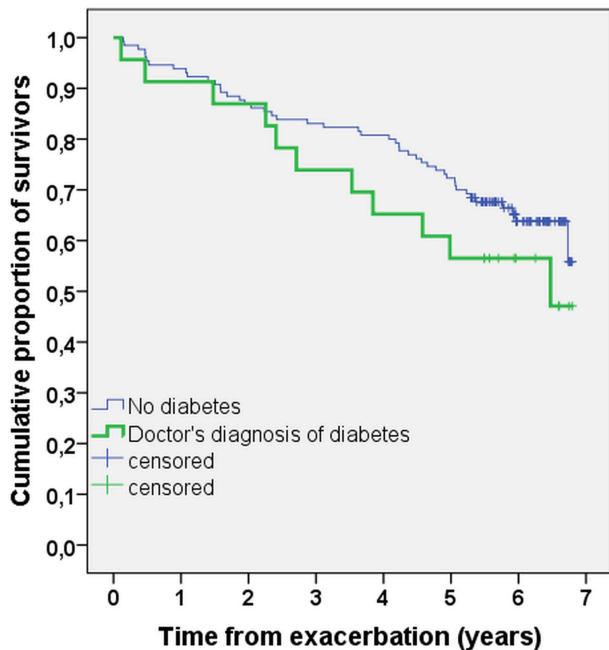†Adjusted HR is calculated per 1 mmol/L of plasma glucose.

Figure 2 Kaplan–Meier plot showing long-term survival after exacerbation in patients with and without doctor's diagnosis of diabetes.

underlying causes of death are shown in table 4. There were no statistically significant differences in the causes between the subgroups (p=0.60).

DISCUSSION

The primary finding of the present study was that doctor's diagnosis of diabetes is a more important predictor of late mortality than plasma glucose levels during mild to moderate obstructive lung disease exacerbation. Doctor's diagnosis of diabetes was associated with a threefold, statistically significant increased risk of late death. Although the elevated plasma glucose levels were also associated with late mortality, these associations were mainly explained by the patients with diabetes who often showed severe hyperglycaemia during the exacerbations. This study also showed that screening diabetes, defined as HbA1c ≥6.5%, in patients without doctor's diagnosis of diabetes is not associated with late mortality in patients with obstructive lung diseases. Finally, we could not find evidence about survival benefit by metformin medication among patients with diabetes.

The present study has two methodological advantages compared with previous studies on the prognostic significance of hyperglycaemia or diabetes. The first is the careful way the hyperglycaemia was detected, with seven plasma glucose measurements during the first day on ward, including night-time measurements. Plasma glucose levels vary markedly within a day during an acute illness[1][17] and a single measurement, such as taken in many previous studies,[7][18–22] can easily miss the highest values. The second advantage is the definition of diabetes including not only a doctor's diagnosis but also the presence of admission HbA1c ≥6.5% (the screening diabetes). It is well known that a substantial proportion of patients with diabetes have not been diagnosed.[15] Indeed, there were 23 patients in the present population with a doctor's diagnosis of diabetes but in further 20 patients the admission HbA1c was ≥6.5%. This is an established way to diagnose diabetes.[15] Thus, in the present study, the common problem of diabetes underdiagnosis was probably mainly overcome.

All patients received inhaled β-2-adrenergic bronchodilators and oral glucocorticoids in internationally recommended doses.[1][23][24] Both drugs are potent inducers of hyperglycaemia.[2–4] Given the very high prevalence of hyperglycaemia during obstructive lung disease exacerbations, we have previously speculated that its main inducer is the received medication, not poor health status or severity of exacerbation.[1] The present findings showing very modest associations between plasma glucose values and late mortality support this view. Furthermore, within the patients without diabetes, the presence of fasting or postprandial hyperglycaemia showed no association with late mortality (aHRs 0.92 to 1.04). These findings contrast with those in patients with pneumonia but without diabetes in whom pneumonia-associated postprandial hyperglycaemia has been shown to be associated with a strong, statistically significant elevated risk of late death (aHR 2.56).[25] In this respect, obstructive lung disease exacerbation-associated hyperglycaemia seems to have less clinical importance than pneumonia-associated hyperglycaemia.

The present study corroborated the previous findings among patients with COPD[8][9] by showing that a pre-exacerbation doctor's diagnosis of diabetes is strongly associated with late mortality. On the contrary, screening diabetes did not relate to late mortality at all. The patients of the two diabetes groups differed substantially; the patients with doctor's diagnosis of diabetes showed

Group	Cancer	Cardiovascular	Obstructive lung diseases	Miscellaneous
No diabetes (N=110, 38 deaths (34%))	7 (8%)	9 (24%)	19 (50%)	3 (8%)
Doctor's diagnosis of diabetes (N=23, 11 deaths (48%))	2 (18%)	5 (46%)	4 (36%)	0 (0%)
Screening diagnosis of diabetes (N=20, 8 deaths (40%))	2 (25%)	1 (12%)	5 (62%)	0 (0%)
All patients (N=153, 57 deaths (37%))	11 (19%)	15 (26%)	28 (49%)	3 (5%)

Table 4 The underlying causes of death

all the typical features of type 2 diabetes: family history of diabetes, large waist circumference and high BMI.[26] On the contrary, the patients with screening diabetes did not differ from the patients without any diabetes in these respects. The typical patient with screening diabetes was a smoker with COPD and suffered from marked hypoxia. It is known that hypoxia causes glucose intolerance, possibly via elevated release of epinephrine.[27] Smoking, in turn, can induce insulin resistance even in patients without diabetes.[28] Nicotine inhibits high-glucose-induced insulin release through a direct effect on nicotinic acetylcholine receptors in pancreatic islets and β cells.[29] Perhaps these 'non-diabetic mechanisms' explain the elevated levels of HbA1c in our patients with screening diabetes and the fact that screening diabetes showed no association with late mortality. In any case, our results highlight the difficulties in diabetes diagnostics among smoking, hypoxic lung patients.

Owing to a recent retrospective study suggesting survival benefit by the diabetes drug metformin in patients with COPD,[10] we investigated its association with late mortality in the present material. We could not demonstrate a protective effect. In fact, the multivariate analysis with comprehensive confounding suggested an increased risk of late death in patients receiving metformin. One possible reason for this discrepancy is the fact that the present study mainly included patients with asthma. Furthermore, metformin is the first-line drug for type 2 diabetes and, therefore, the findings observed herein may also reflect uncovered residual confounding about clinical conditions, why patients were not prescribed metformin instead of other therapies. We stress that the association between metformin and late mortality was not the main objective of the present study and that the patient numbers are far too small to draw any conclusions about the safety of metformin in patients with asthma. More studies about the safety of metformin in patients with obstructive lung diseases are needed.

The main limitation of the present study is the relatively small number of patients, which may cause type II statistical errors. Furthermore, the population did not include patients who were confused and patients who needed treatment in the intensive care unit. The present population thus consists of patients with mild to moderate exacerbations and the results cannot be generalised to all hospitalised exacerbation patients. On the other hand, the present patients with asthma were probably older and were more often smokers than average. The pooling of patients with asthma and COPD together may also raise criticism. This was considered justified since all patients were subjected to the same, strong hyperglycaemia inducers, namely high doses of inhaled β-2-adrenergic bronchodilators and oral glucocorticoids. Furthermore, there is considerable overlap between asthma and COPD and it is often impossible to differentiate them in an emergency setting.[30 31] In the present study, the attending physician was asked which of the conditions was the dominant in each case. The lack of spirometric data precludes objective separation of the two conditions and it can also be regarded as a weakness in the present study. To minimise the possible bias of patient pooling, COPD was included in the multivariate analysis.

In conclusion, the present study showed that long-term mortality after exacerbation of obstructive lung disease is strongly affected by the history of diabetes. Neither admission HbA1c nor glucose levels during exacerbation added essential information. Thus, these measurements seem to be unnecessary when estimating long-term mortality.

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