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The long-term mortality after community-acquired pneumonia: Impacts of diabetes and newly discovered hyperglycaemia. A prospective, observational cohort study.

Running title: Pneumonia and hyperglycaemia

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ABSTRACT

Objectives Community-acquired pneumonia is associated with a significant long-term mortality after initial recovery. It has been acknowledged that additional research is urgently needed to examine the contributors to this long-term mortality. The objective of the present study was to assess whether diabetes or newly discovered hyperglycaemia during pneumonia affects the long-term mortality.

Design: A prospective, observational cohort study

Setting: A single secondary centre in eastern Finland

Participants: 153 consecutive hospitalised patients who survived at least 30 days after mild to moderate community-acquired pneumonia.

Interventions: Plasma glucose levels were recorded seven times during the first day on the ward. Several possible confounders were also recorded. The surveillance status and causes of death were recorded after median of five years and eleven months.

Results In multivariate Cox regression analysis, a previous diagnosis of diabetes among the whole population (adjusted hazard ratio 2.84 (1.35 – 5.99)) and new postprandial hyperglycaemia among the non-diabetic population (adjusted hazard ratio 2.56 (1.04 – 6.32)) showed independent associations with late mortality. New fasting hyperglycaemia was not an independent predictor. The mortality rates at the end of follow-up were 54 %, 37 %, and 10 % among patients with diabetes, non-diabetic patients with new postprandial hyperglycaemia, and non-diabetic patients without postprandial hyperglycaemia, respectively ($p < 0.001$). The underlying causes of death roughly mirrored those in Finnish general population with a slight excess in mortality due to chronic respiratory diseases. Pneumonia was the immediate cause of death in just 8 % of all late deaths.

Conclusions A previous diagnosis of diabetes and newly discovered postprandial hyperglycaemia increase the risk of death for several years after community-acquired pneumonia. As the knowledge about patient subgroups with an increased late mortality risk is gradually gathering, more studies are needed to evaluate the possible post-pneumonia interventions to reduce the late mortality.

Strengths and limitations of the study

- The plasma glucose levels were carefully measured during pneumonia 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 is the lack of validated pneumonia severity scoring although several pneumonia severity-related variables were collected
- The present population consists of patients with mild to moderate CAP. Therefore, the results cannot be generalised to all hospitalised pneumonia patients.

INTRODUCTION

Pneumonia is the leading cause of infectious death worldwide with 3.2 million annual victims.[1] This figure, which is impressive enough *per se*, only contains the acute mortality. Pneumonia is also associated with significant late mortality up to several years afterwards among patients who survive the initial episode. In a large population-based cohort study, the mortality rate was 53 % at five years after an episode of community-acquired pneumonia (CAP).[2] Importantly, the long-term mortality is substantially higher than that of either the general population or a control population hospitalised for reasons other than CAP.[3-5] Given the high and rising incidence of CAP, its long-acting effect on mortality should be regarded as major public health threat.[6 7] It has been acknowledged that additional research is urgently needed to examine the contributors to this long-term mortality.[8]

Probably the most consistently identified contributor to late mortality after CAP is the presence of comorbid conditions, especially neurodegenerative disorders, cardiovascular conditions, malignancy, and chronic obstructive lung disease.[7] To the best of our knowledge, diabetes has not been investigated in this respect. Yende *et al*. analysed two large CAP cohorts and found out that diabetes increased the mortality rate within the first year after CAP with unadjusted hazard ratios (HR) of 1.4 - 1.9.[9] They suggested that the higher mortality may be due to worsening of pre-existing cardiovascular disease or higher risk of acute kidney injury. However, the early and late deaths were not analysed separately and the follow-up time was relatively short.

Hyperglycaemia is associated with short-term mortality in several acute disorders including CAP.[10-14] In pneumonia, a newly detected hyperglycaemia among non-diabetic patients seems to increase the short-term mortality rate more than hyperglycaemia among diabetic patients.[13] The impact of new, pneumonia-associated hyperglycaemia on the long-term mortality has not been investigated. The objective of the present study was to assess whether diabetes or newly discovered hyperglycaemia among non-diabetics affects the late mortality after CAP.

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 CAP were recruited. The patients were considered to have pneumonia if they had an acute febrile illness with a new radiographic shadowing. During that time 245 patients were hospitalised because of pneumonia (figure 1). Patients were excluded from this study if they had severe pneumonia requiring treatment in the intensive care unit, if they could not give informed consent due to confusion, or if their antibiotic treatment had already been started on another institution. Altogether 92 patients were excluded and 153 patients included. All the 153 patients survived at least 30 days after admission. Among them, 22 had a previous diagnosis of diabetes (table 1).

Measurements during pneumonia

During the first 24 hours on the ward the plasma glucose was determined seven times, at three o'clock at night, before breakfast, before lunch, after lunch, before dinner, after dinner, and at bedtime. In addition, the family history for diabetes and the pre-pneumonia Karnofsky performance score were assessed. Height, weight, waist circumference, oxygen saturation, blood pressure, temperature, and heart rate were measured. Blood tests included glycosylated haemoglobin A1c (HbA1c), N-terminal pro B-type natriuretic peptide (NT-proBNP), C-reactive protein, leukocytes, urea, and arterial blood gas analysis.

The detailed description of the methods and the baseline results have been published.[15] 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 associate with pneumonia prognosis.[16] It was measured from the blood sample collected at admission utilising a commercially available electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). 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.[17]

Table 1. Patient characteristics

	Diabetic patients (N = 22)	p[a]	Patients without diabetes (N = 131)		p[b]	Patients with missing data
			Postprandial hyper-glycaemia (n = 43)	No postprandial hyperglycaemia (n = 88)		
Age, yrs	66 (59 - 73)	0.04	66 (60 - 71)	53 (49 - 58)	0.001	0
Male gender	68 %	0.40	67 %	54 %	0.16	0
Family history of diabetes	68 %	0.004	47 %	30 %	0.07	14
BMI, kg/m2	33 (28 - 37)	0.001	27 (25 - 29)	27 (26 - 29)	0.56	0
Waist circumference, cm	110 (102 - 118)	<0.001	100 (95 - 104)	97 (94 - 100)	0.27	18
gHbA1c, %	7.83 (6.97 - 8.69)	<0.001	6.12 (5.79 - 6.44)	5.64 (5.53 - 5.76)	<0.001	7
Karnofsky 80% or less	50 %	0.02	44 %	16 %	<0.001	0
Three or more comorbidities	54 %	<0.001	23 %	14 %	0.17	0
Diastolic blood pressure, mmHg	75 (69 - 81)	0.12	81 (75 - 86)	80 (77 - 84)	0.99	1
Heart rate, 1/min	99 (90 - 109)	0.22	100 (92 - 107)	91 (86 - 95)	0.005	1
Oxygen saturation (%)	92 (89 - 94)	0.35	91 (89 - 93)	94 (93 - 95)	0.004	13
Leukocytes, 10^9/l	11.8 (9.6 - 13.9)	0.46	12.4 (10.6 - 14.3)	11.7 (10.1 - 13.3)	0.10	0
Urea , mmol/l	6.88 (4.96 - 8.79)	0.28	8.61 (6.41 - 10.8)	4.72 (4.00 - 5.44)	<0.001	11
CRP, mg/l	164 (119 - 209)	0.97	228 (166 - 289)	146 (127 - 165)	<0.001	1
Elevated NT-proBNP	32 %	0.51	29 %	23 %	0.47	4
Length of hospital stay, days	5.8 (4.6 - 7.1)	0.53	6.6 (5.7 - 7.5)	5.9 (5.2 - 6.6)	0.03	1

BMI, body mass index; gHbA1c, glycosylated haemoglobin A1c expressed as percentage of total haemoglobin; CRP, C-reactive protein; NT-proBNP, plasma N-terminal pro B-type natriuretic peptide. The data is presented either as percentage of patients showing the feature or means (95 % confidence intervals)

[a] p value indicates the differences between diabetic and non-diabetic patients

[b] p value indicates the differences between the patients with and without postprandial hyperglycaemia within the non-diabetic patients.

Definitions

Diabetes was defined as doctor's diagnosis of diabetes which had been set before the current pneumonia episode, and verified from the patient files. New hyperglycaemia was defined as hyperglycaemia during the first 24 hours of pneumonia hospitalisation in a patient without a doctor's diagnosis of diabetes. Fasting hyperglycaemia was defined as hyperglycaemia detected at three o'clock at night or at seven o'clock in the morning before breakfast. Postprandial hyperglycaemia was defined as hyperglycaemia detected during the daytime or in the evening. The main outcome variable was mortality from 30 days after pneumonia up to the end of follow-up. The predictor variables were diabetes, new fasting hyperglycaemia, and new postprandial hyperglycaemia. A confounder was a variable which showed an association with both the plasma glucose levels during pneumonia and the late mortality. However, a potential confounder with a causal relationship to the outcome variable was not included. Furthermore, if two potential confounders were closely interrelated, the one with a closer association with the plasma glucose levels was included.

Follow-up after pneumonia

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 version 10, were obtained from death certificates. The median follow-up was five years and eleven months.

Ethics

The study was reviewed by the Research Ethic Committee, Hospital District of Northern Savo (75//2006) and it was performed in accordance with the ethical standards laid down on the 2000 Declaration of Helsinki. All patients gave their written informed consent.

Statistical analysis

Comparative survival curves were constructed using Kaplan-Meier methodology. The unadjusted HRs were assessed utilising univariate Cox regression analysis. Continuous data was divided to quartiles. The assumption of proportional hazard was checked by graphically comparing the hazard curves. To determinate the adjusted HRs for diabetes, new fasting hyperglycaemia and new postprandial hyperglycaemia, Cox multivariate regression analysis with backwards directed stepwise procedure was utilised. In this analysis patients with missing data were excluded.

The analysis about the effect of new hyperglycaemia was restricted to the 131 non-diabetic pneumonia patients. Among them, receiver operator curves (ROC) were produced for both fasting and postprandial plasma glucose values to define the best cut-off values to predict death during the follow-up.

Frequency comparison was performed by Chi-squared test. Student's T-test and Pearson correlation coefficient were utilised when appropriate. Categorical data is expressed as percentages and continuous data as means and 95 % confidence intervals (CI). 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

Univariate analysis and the ROC analysis

Table 1 shows the numbers of patients in each subgroup and their characteristics. The following features showed a statistically significant association with the late mortality within the whole population: Presence of diabetes (HR 3.5 (1.7 - 6.9), figure 2), advanced age, Karnofsky score equal or less than 80 %, presence of three or more co-morbidities, low diastolic blood pressure, low arterial blood oxygen saturation, high urea, NT-proBNP above predicted value[17], high gHbA1c, and long hospital stay (data not shown). The proportional hazards remained constant over time.

Among the non-diabetic patients, the ROC analysis of the fasting plasma glucose measurements revealed that the level of 7.05 mmol/l was the best cut-off value to predict late mortality (results not shown). A glucose level exceeding it showed an unadjusted HR of 2.7 (1.1 – 6.4) (p = 0.027). 52 % of the non-diabetic patients showed a fasting glucose level exceeding 7.05 mmol/l. In one patient, no fasting glucose values were obtained. The ROC analysis of the postprandial glucose measurements revealed that the level of 10.75 mmol/l was the best cut-off value (results not shown). The corresponding unadjusted HR was 4.2 (1.9 – 9.6) (p = 0.001, figure 2). 33 % of the non-diabetic patients showed a postprandial glucose level exceeding 10.75 mmol/l. Utilising these plasma glucose cut-off values among the 22 diabetic patients it could be shown that 19 of them (86 %) showed fasting hyperglycaemia and 18 (82 %) showed postprandial hyperglycaemia.

Multivariate analysis

The following confounders were included: Age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. The results of the multivariate Cox regression analysis are shown in tables 2 and 3. It can be seen that a diagnosis of diabetes among the whole population (table 2) and new postprandial hyperglycaemia among the non-diabetic population (table 3) showed independent associations with late mortality after pneumonia. New fasting hyperglycaemia was not a predictor of mortality when the confounders were taken into account (p = 0.74).

The mortality rates and the causes of death

The mortality rates at the end of follow-up were 54 %, 37 %, and 10 % among patients with diabetes, non-diabetic patients with new postprandial hyperglycaemia, and non-diabetic patients without postprandial hyperglycaemia, respectively (p < 0.001). The underlying causes of death are shown in table 4. The immediate causes of death mirrored the underlying causes. Pneumonia was the immediate cause of death in just three cases (8 % of all deaths).

Table 2. Cox multivariate regression analysis with backward directed stepwise procedure about the effect of diabetes on the risk of late death after pneumonia. The included confounders were age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. Only factors with at least suggestive independent association ($p < 0.10$) with the risk of late death are presented. N = 153

	Adjusted hazard ratio	**95 % CI**	**P value**
Diabetes	2.84	1.35 – 5.99	0.006
Karnofsky equal or less than 80%	4.19	1.86 – 9.46	0.001
Age, years	1.53*	1.00 – 2.34	0.048
Urea, mmol/L	1.78*	1.20 - 2.64	0.004

*Hazard ratio is expressed per quartile

Table 3. Cox multivariate regression analysis with backward directed stepwise procedure about the effect of new postprandial hyperglycaemia on the risk of late death after pneumonia. The included confounders were age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. Only factors with at least suggestive independent association ($p < 0.10$) with the risk of late death are presented. N = 131

	Adjusted hazard ratio	**95 % CI**	**P value**
New postprandial hyperglycaemia	2.56	1.04 – 6.32	0.041
Karnofsky equal or less than 80%	3.26	1.12 – 9.47	0.030
Age, years	1.97*	1.14 – 3.39	0.015

*Hazard ratio is expressed per quartile

Table 4. The underlying causes of late death

Group	Cancer	Cardiovascular	Obstructive lung diseases	Miscellaneous
No diabetes, no postprandial hyperglycaemia (9 deaths)	2 (22 %)	4 (44 %)	0 (0 %)	3 (33 %)
No diabetes, with postprandial hyperglycaemia (16 deaths)	1 (6 %)	4 (25 %)	7 (44 %)	4 (25 %)
Diabetes (11 deaths)	3 (27 %)	6 (54 %)	0 (0 %)	2 (18 %)
All patients (36 deaths)	6 (17 %)	14 (39 %)	7 (19 %)	9 (25 %)

DISCUSSION

The present study confirms that both the pre-pneumonia health status and the severity of pneumonia are associated with the late mortality after CAP.[7] Both of them could be taken into account in the present study. It showed that a pre-pneumonia diagnosis of diabetes is associated with a three-fold increase in the risk of death up to six years after mild to moderate CAP. The study thus corroborates and extends the findings of Yende et al, who reported of increased mortality rates in diabetic patients up to one year after pneumonia.[9] The present study also demonstrated that new postprandial hyperglycaemia among non-diabetic patients shows an independent association with late mortality after pneumonia. Such an association has not been described earlier.

In acute illnesses, complex mechanisms involving hormones and cytokines lead to hyperglycaemia which is mainly caused by excessive hepatic glucose production and manifested by high fasting glucose values.[12] This probably explains our finding that fasting hyperglycaemia was more common than postprandial hyperglycaemia among the non-diabetic CAP patients. As fasting hyperglycaemia was not an independent predictor of mortality in the present study, it may be regarded as an adequate body response to infection. Postprandial hyperglycaemia, in turn, is considered as the first step in the deterioration of glucose homeostasis.[18] In the present study, the survival curves of the diabetic patients and the non-diabetic patients with postprandial hyperglycaemia were almost identical up to 2.5 years. There is evidence suggesting that postprandial hyperglycaemia is an independent risk factor for cardiovascular disease, stroke, retinopathy, renal failure, and neurologic complications in both diabetic and non-diabetic individuals.[18] Excess late mortality after CAP can now be added to that list.

One may suspect that the hyperglycaemic patients without a previous, doctor's diagnosis of diabetes may actually have suffered from diabetes without knowing it. HbA1c reflects mean blood glucose levels during the previous 2 – 3 months and can be used to diagnose diabetes.[19] It is true that the HbA1c values were higher in the non-diabetic patients with new postprandial hyperglycaemia than in those without it. However, the 95 % confidence interval of their HbA1c values was below 6.5 % which is considered diagnostic for diabetes[19] and also well below the HbA1c values of the diabetic patients. In addition, the patients with new postprandial hyperglycaemia did not differ from the euglycaemic non-diabetic patients with respect to family history of diabetes, body mass index, or waist circumference. On the contrary, the patients with a doctor's diagnosis of diabetes clearly differed from the rest of the population by showing all these typical features of type 2 diabetes.[20] Therefore, most of the CAP patients with new postprandial hyperglycaemia probably did not have an undiagnosed diabetes before pneumonia. This supports the view that stress hyperglycaemia and diabetes are two separate disorders.[12 15 21]

The commonly used plasma glucose cut-off values for transient hyperglycaemia during illness (stress hyperglycaemia) have been adopted from the diabetes diagnostics (fasting glucose > 6.9 mmol/l or random glucose > 11.1 mmol/l).[12] To our knowledge, they have not been validated in non-diabetic patients with acute illnesses. The present material allowed us to define cut-off values that showed the best predictive power for late mortality after CAP among the non-diabetic patients: 7.05 mmol/l for fasting glucose and 10.75 mmol/l for postprandial glucose. Our values were surprisingly close to those adopted from diabetes diagnostics and thus support their use also among non-diabetic patients with stress hyperglycaemia.

The present paper provides some new information how to identify patients at increased risk of death late after CAP. However, it is not known whether the identification of such patients can influence their long-term prognosis. Streptococcus pneumonia vaccination after CAP may be of limited value since just 8 % of all late deaths were caused by pneumonia in the present study. This is in accordance with a larger study in which just 6 % of short-term survivors from CAP finally died of pneumonia.[5] The underlying causes of death in the present population roughly mirrored those in Finnish general population [22] with one exception: In the general population, the proportion of a chronic lung disease as the underlying cause of death is 4 % but in the present population it was 19 %. The above-mentioned Dutch study reported exactly the same finding with much higher numbers of deaths.[5] This may be, at least partly, due to patients with obstructive lung diseases being prone to catch CAP and prone to be hospitalised in case of CAP.[23]

If the possibilities for secondary interventions are to be established, the focus should perhaps be in the primary prevention of pneumonia. The present study suggests that pneumococcus vaccination should be focused on diabetic patients, aged patients, and those with low performance status, among other groups previously reported to show an excessive long-term mortality after pneumonia.[7 24]

The main strength of the present study was the careful way to detect hyperglycaemia during pneumonia with seven plasma glucose measurements during the first day on ward, also including night-time measurements. Most previous studies about the effects of hyperglycaemia on pneumonia prognosis are handicapped by the small number, usually one, of plasma glucose measurements. Plasma glucose levels vary markedly within a day during an acute illness and a single measurement can easily miss the highest values.[15 21] Frequent glucose measurements explain the higher prevalence of new hyperglycaemia in the present study compared with the previous ones.[10 11] The prospective nature and the comprehensive collection of information about possible confounders may also be considered as strengths.

The main limitation of the present study was the lack of validated pneumonia severity scoring. However, many severity-related variables like oxygen saturation, temperature, blood pressure, heart rate, C-reactive protein, leukocytes, urea, and arterial blood gas analysis, were recorded. The population did not include patients who were confused and patients who needed treatment in intensive care unit. The present

population thus consists of patients with mild to moderate CAP. Therefore, the results cannot be generalised to all hospitalised pneumonia patients.

In conclusion, a previous diagnosis of diabetes and newly discovered postprandial hyperglycaemia increase the risk of death for several years after CAP. As the knowledge about patient subgroups with an increased late mortality risk is gradually gathering, more studies are needed to evaluate the possible post-pneumonia interventions to reduce the late mortality.

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Competing interests

The authors have no competing interests

Ethics approval

The study was reviewed by the Research Ethic Committee, Hospital District of Northern Savo (75//2006) and it was performed in accordance with the ethical standards laid down on the 2000 Declaration of Helsinki. All patients gave their written informed consent.

Contributions

Heikki Koskela has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; He has written the article and is the guarantor.

Päivi Salonen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. She has revised the article critically for important intellectual content and provided final approval of the version to be published.

Jarkko Romppanen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. He has revised the article critically for important intellectual content and provided final approval of the version to be published.

Leo Niskanen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. He has revised the article critically for important intellectual content and provided final approval of the version to be published.

Data sharing statement

Extra data is available by emailing Heikki Koskela

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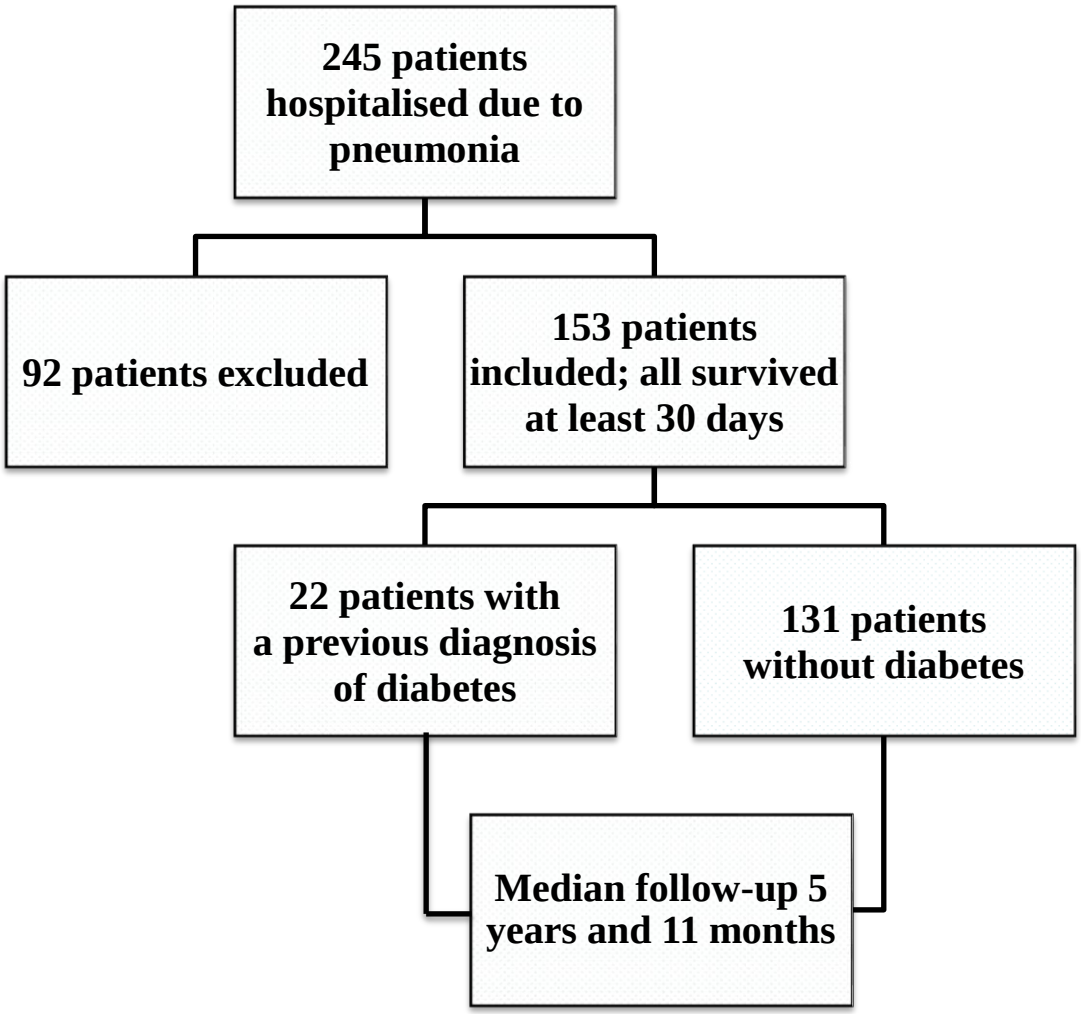
FIGURE LEGENDS

Figure 1. Inclusion of the patients. Patients were excluded from this study if they had severe pneumonia requiring treatment in the intensive care unit, if they could not give informed consent due to confusion, or if their antibiotic treatment had already been started on another institution.

Figure 2. Kaplan-Meier plot showing long-term survival after community-acquired pneumonia among patients with diabetes (N = 22), non-diabetic patients with new postprandial hyperglycaemia (N = 43), and non-diabetic patients without postprandial hyperglycaemia (N = 88). $P < 0.001$ between the groups.


245 patients hospitalised due to pneumonia
92 patients excluded
153 patients included; all survived at least 30 days
22 patients with a previous diagnosis of diabetes
131 patients without diabetes
Median follow-up 5 years and 11 months

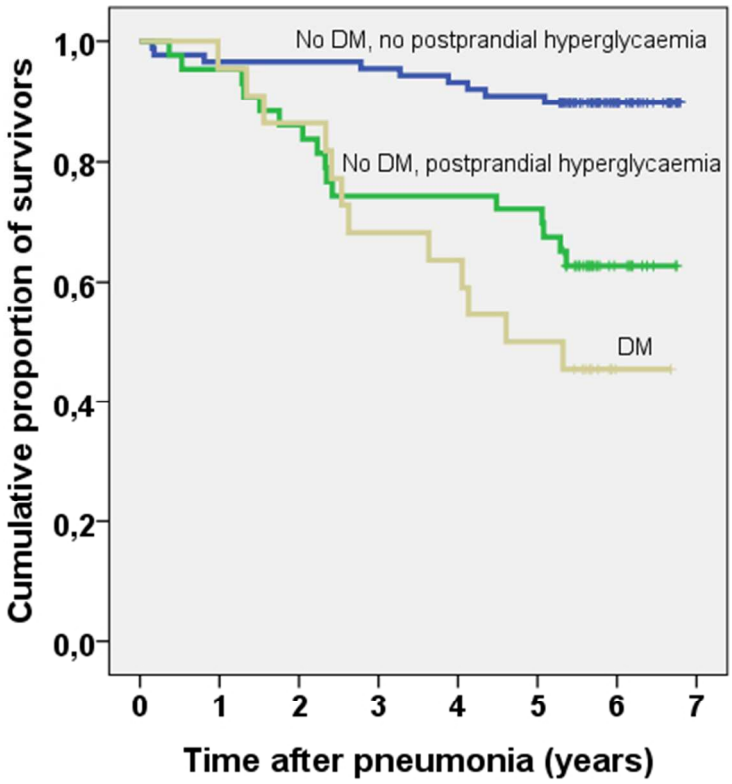


Figure 2
220x176mm (72 x 72 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract PAGES 1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found PAGE 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported PAGE 4
Objectives	3	State specific objectives, including any prespecified hypotheses PAGE 4
Methods		
Study design	4	Present key elements of study design early in the paper PAGE 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection PAGE 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up PAGE 5 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable PAGE 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group PAGE 5
Bias	9	Describe any efforts to address potential sources of bias PAGES 13,14
Study size	10	Explain how the study size was arrived at PAGE 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why PAGES 7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding PAGES 7,8
		(*b*) Describe any methods used to examine subgroups and interactions PAGES 7,9
		(*c*) Explain how missing data were addressed PAGE 8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed NO LOSS TO FOLLOW-UP *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses PAGE 8

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed PAGE 5
		(b) Give reasons for non-participation at each stage PAGE 5
		(c) Consider use of a flow diagram FIGURE 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders TABLE 1
		(b) Indicate number of participants with missing data for each variable of interest TABLE 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) PAGE 7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time PAGE 7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included PAGES 8,9, TABLES 2, 3
		(*b*) Report category boundaries when continuous variables were categorized PAGE 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period PAGE 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses PAGE 10
Discussion		
Key results	18	Summarise key results with reference to study objectives PAGE 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias PAGES 13,14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence PAGE 14
Generalisability	21	Discuss the generalisability (external validity) of the study results PAGES 13, 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based PAGE 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The long-term mortality after community-acquired pneumonia: Impacts of diabetes and newly discovered hyperglycaemia. A prospective, observational cohort study.

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The long-term mortality after community-acquired pneumonia: Impacts of diabetes and newly discovered hyperglycaemia. A prospective, observational cohort study.

Running title: Pneumonia and hyperglycaemia

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ABSTRACT

Objectives Community-acquired pneumonia is associated with a significant long-term mortality after initial recovery. It has been acknowledged that additional research is urgently needed to examine the contributors to this long-term mortality. The objective of the present study was to assess whether diabetes or newly discovered hyperglycaemia during pneumonia affects the long-term mortality.

Design: A prospective, observational cohort study

Setting: A single secondary centre in eastern Finland

Participants: 153 consecutive hospitalised patients who survived at least 30 days after mild to moderate community-acquired pneumonia.

Interventions: Plasma glucose levels were recorded seven times during the first day on the ward. Several possible confounders were also recorded. The surveillance status and causes of death were recorded after median of five years and eleven months.

Results In multivariate Cox regression analysis, a previous diagnosis of diabetes among the whole population (adjusted hazard ratio 2.84 (1.35 – 5.99)) and new postprandial hyperglycaemia among the non-diabetic population (adjusted hazard ratio 2.56 (1.04 – 6.32)) showed independent associations with late mortality. New fasting hyperglycaemia was not an independent predictor. The mortality rates at the end of follow-up were 54 %, 37 %, and 10 % among patients with diabetes, non-diabetic patients with new postprandial hyperglycaemia, and non-diabetic patients without postprandial hyperglycaemia, respectively ($p < 0.001$). The underlying causes of death roughly mirrored those in Finnish general population with a slight excess in mortality due to chronic respiratory diseases. Pneumonia was the immediate cause of death in just 8 % of all late deaths.

Conclusions A previous diagnosis of diabetes and newly discovered postprandial hyperglycaemia increase the risk of death for several years after community-acquired pneumonia. As the knowledge about patient subgroups with an increased late mortality risk is gradually gathering, more studies are needed to evaluate the possible post-pneumonia interventions to reduce the late mortality.

Strengths and limitations of the study

- The plasma glucose levels were carefully measured during pneumonia 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 is the lack of validated pneumonia severity scoring although several pneumonia severity-related variables were collected
- The present population consists of patients with mild to moderate CAP. Therefore, the results cannot be generalised to all hospitalised pneumonia patients.

INTRODUCTION

Pneumonia is the leading cause of infectious death worldwide with 3.2 million annual casualties.[1] This figure, which is impressive enough *per se*, only contains the acute mortality. Pneumonia is also associated with significant late mortality up to several years afterwards among patients who survive the initial episode. In a large population-based cohort study, the mortality rate was 53 % at five years after an episode of community-acquired pneumonia (CAP).[2] Importantly, the long-term mortality is substantially higher than that of either the general population or a control population hospitalised for reasons other than CAP.[3-5] Given the high and rising incidence of CAP, its long-acting effect on mortality should be regarded as major public health threat.[6 7] It has been acknowledged that additional research is urgently needed to examine the contributors to this long-term mortality.[8]

Probably the most consistently identified contributor to late mortality after CAP is the presence of comorbid conditions, especially neurodegenerative disorders, cardiovascular conditions, malignancy, and chronic obstructive lung disease.[7] To the best of our knowledge, diabetes has not been investigated in this respect. Yende *et al*. analysed two large CAP cohorts and found out that diabetes increased the mortality rate within the first year after CAP with unadjusted hazard ratios (HR) of 1.4 - 1.9.[9] They suggested that the higher mortality may be due to worsening of pre-existing cardiovascular disease or higher risk of acute kidney injury. However, the early and late deaths were not analysed separately and the follow-up time was relatively short.

Hyperglycaemia is associated with short-term mortality in several acute disorders including CAP.[10-14] In pneumonia, a newly detected hyperglycaemia among non-diabetic patients seems to increase the short-term mortality rate more than hyperglycaemia among diabetic patients.[13] The impact of new, pneumonia-associated hyperglycaemia on the long-term mortality has not been investigated. The objective of the present study was to assess whether diabetes or newly discovered hyperglycaemia among non-diabetics affects the late mortality after CAP.

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 CAP were recruited. The patients were considered to have pneumonia if they had an acute febrile illness with a new radiographic shadowing. During that time 245 patients were hospitalised because of pneumonia (figure 1). Patients were excluded from this study if they had severe pneumonia requiring treatment in the intensive care unit, if they could not give informed consent due to confusion, or if their antibiotic treatment had already been started on another institution. Altogether 92 patients were excluded and 153 patients included. All the 153 patients survived at least 30 days after admission. Among them, 22 had a previous diagnosis of diabetes (table 1).

Measurements during pneumonia

During the first 24 hours on the ward the plasma glucose was determined seven times, at three o'clock at night, before breakfast, before lunch, after lunch, before dinner, after dinner, and at bedtime. In addition, the family history for diabetes and the pre-pneumonia Karnofsky performance score were assessed. Karnofsky score is a general measure of patient independence which has most often utilised in patients with cancer.[15 16] Height, weight, waist circumference, oxygen saturation, blood pressure, temperature, and heart rate were measured. Blood tests included glycosylated haemoglobin A1c (HbA1c), N-terminal pro B-type natriuretic peptide (NT-proBNP), C-reactive protein, leukocytes, urea, and arterial blood gas analysis.

The detailed description of the methods and the baseline results have been published.[17] 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 associate with pneumonia prognosis.[18] It was measured from the blood sample collected at admission utilising a commercially available electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). 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.[19]

Table 1. Patient characteristics

	Diabetic patients (N = 22)	p[a]	Patients without diabetes (N = 131)		p[b]	Patients with missing data
			Postprandial hyper-glycaemia (n = 43)	No postprandial hyperglycaemia (n = 88)		
Age, yrs	66 (59 - 73)	0.04	66 (60 - 71)	53 (49 - 58)	0.001	0
Male gender	68 %	0.40	67 %	54 %	0.16	0
Family history of diabetes	68 %	0.004	47 %	30 %	0.07	14
BMI, kg/m2	33 (28 - 37)	0.001	27 (25 - 29)	27 (26 - 29)	0.56	0
Waist circumference, cm	110 (102 - 118)	<0.001	100 (95 - 104)	97 (94 - 100)	0.27	18
gHbA1c, %	7.83 (6.97 - 8.69)	<0.001	6.12 (5.79 - 6.44)	5.64 (5.53 - 5.76)	<0.001	7
Karnofsky 80% or less	50 %	0.02	44 %	16 %	<0.001	0
Three or more comorbidities	54 %	<0.001	23 %	14 %	0.17	0
Diastolic blood pressure, mmHg	75 (69 - 81)	0.12	81 (75 - 86)	80 (77 - 84)	0.99	1
Heart rate, 1/min	99 (90 - 109)	0.22	100 (92 - 107)	91 (86 - 95)	0.005	1
Oxygen saturation (%)	92 (89 - 94)	0.35	91 (89 - 93)	94 (93 - 95)	0.004	13
Leukocytes, 10^9/l	11.8 (9.6 - 13.9)	0.46	12.4 (10.6 - 14.3)	11.7 (10.1 - 13.3)	0.10	0
Urea , mmol/l	6.88 (4.96 - 8.79)	0.28	8.61 (6.41 - 10.8)	4.72 (4.00 - 5.44)	<0.001	11
CRP, mg/l	164 (119 - 209)	0.97	228 (166 - 289)	146 (127 - 165)	<0.001	1
Elevated NT-proBNP	32 %	0.51	29 %	23 %	0.47	4
Length of hospital stay, days	5.8 (4.6 - 7.1)	0.53	6.6 (5.7 - 7.5)	5.9 (5.2 - 6.6)	0.03	1

BMI, body mass index; gHbA1c, glycosylated haemoglobin A1c expressed as percentage of total haemoglobin; CRP, C-reactive protein; NT-proBNP, plasma N-terminal pro B-type natriuretic peptide. The data is presented either as percentage of patients showing the feature or means (95 % confidence intervals)

[a] p value indicates the differences between diabetic and non-diabetic patients

[b] p value indicates the differences between the patients with and without postprandial hyperglycaemia within the non-diabetic patients.

Definitions

Diabetes was defined as doctor's diagnosis of diabetes which had been set before the current pneumonia episode, and verified from the patient files. New hyperglycaemia was defined as hyperglycaemia during the first 24 hours of pneumonia hospitalisation in a patient without a doctor's diagnosis of diabetes. Fasting hyperglycaemia was defined as hyperglycaemia detected at three o'clock at night or at seven o'clock in the morning before breakfast. Postprandial hyperglycaemia was defined as hyperglycaemia detected during the daytime or in the evening. The cut-off values for both fasting and postprandial hyperglycaemia among the non-diabetic patients were those defined by the receiver operator curves (ROC) analysis (see below). The main outcome variable was mortality from 30 days after pneumonia up to the end of follow-up. The predictor variables were diabetes, new fasting hyperglycaemia, and new postprandial hyperglycaemia. A confounder was a variable which showed an association with both the plasma glucose levels during pneumonia and the late mortality. However, a potential confounder with a causal relationship to the outcome variable was not included. Furthermore, if two potential confounders were closely interrelated, the one with a closer association with the plasma glucose levels was included.

Follow-up after pneumonia

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 version 10, were obtained from death certificates. The median follow-up was five years and eleven months.

Ethics

The study was reviewed by the Research Ethic Committee, Hospital District of Northern Savo (75//2006) and it was performed in accordance with the ethical standards laid down on the 2000 Declaration of Helsinki. All patients gave their written informed consent.

Statistical analysis

Comparative survival curves were constructed using Kaplan-Meier methodology. The unadjusted HRs were assessed utilising univariate Cox regression analysis. Continuous data was divided to quartiles. The assumption of proportional hazard was checked by graphically comparing the hazard curves. To determinate the adjusted HRs for diabetes, new fasting hyperglycaemia and new postprandial hyperglycaemia, Cox multivariate regression analysis with backwards directed stepwise procedure was utilised. In this analysis patients with missing data were excluded.

The analysis about the effect of new hyperglycaemia was restricted to the 131 non-diabetic pneumonia patients. Among them, ROC curves were produced for both fasting and postprandial plasma glucose values to define the best cut-off values to predict death during the follow-up.

Frequency comparison was performed by Chi-squared test. Student's T-test and Pearson correlation coefficient were utilised when appropriate. Categorical data is expressed as percentages and continuous data as means and 95 % confidence intervals (CI). 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

Univariate analysis and the ROC analysis

Table 1 shows the numbers of patients in each subgroup and their characteristics. The following features showed a statistically significant association with the late mortality within the whole population: Presence of diabetes (HR 3.5 (1.7 - 6.9), figure 2), advanced age, Karnofsky score equal or less than 80 %, presence of three or more co-morbidities, low diastolic blood pressure, low arterial blood oxygen saturation, high urea,

NT-proBNP above predicted value[19], high gHbA1c, and long hospital stay (data not shown). The proportional hazards remained constant over time.

Among the non-diabetic patients, the ROC analysis of the fasting plasma glucose measurements revealed that the level of 7.05 mmol/l was the best cut-off value to predict late mortality (results not shown). A glucose level exceeding it showed an unadjusted HR of 2.7 (1.1 – 6.4) (p = 0.027). 52 % of the non-diabetic patients showed a fasting glucose level exceeding 7.05 mmol/l. In one patient, no fasting glucose values were obtained. The ROC analysis of the postprandial glucose measurements revealed that the level of 10.75 mmol/l was the best cut-off value (results not shown). The corresponding unadjusted HR was 4.2 (1.9 – 9.6) (p = 0.001, figure 2). 33 % of the non-diabetic patients showed a postprandial glucose level exceeding 10.75 mmol/l. Utilising these plasma glucose cut-off values among the 22 diabetic patients it could be shown that 19 of them (86 %) showed fasting hyperglycaemia and 18 (82 %) showed postprandial hyperglycaemia.

Multivariate analysis

The following confounders were included: Age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. The results of the multivariate Cox regression analysis are shown in tables 2 and 3. It can be seen that a diagnosis of diabetes among the whole population (table 2) and new postprandial hyperglycaemia among the non-diabetic population (table 3) showed independent associations with late mortality after pneumonia. New fasting hyperglycaemia was not a predictor of mortality when the confounders were taken into account (p = 0.74).

The mortality rates and the causes of death

The mortality rates at the end of follow-up were 54 %, 37 %, and 10 % among patients with diabetes, non-diabetic patients with new postprandial hyperglycaemia, and non-diabetic patients without postprandial hyperglycaemia, respectively (p < 0.001). The underlying causes of death are shown in table 4. The immediate causes of death mirrored the underlying causes. Pneumonia was the immediate cause of death in just three cases (8 % of all deaths).

Table 2. Cox multivariate regression analysis with backward directed stepwise procedure about the effect of diabetes on the risk of late death after pneumonia. The included confounders were age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. Only factors with at least suggestive independent association ($p < 0.10$) with the risk of late death are presented. N = 142 (one diabetic and ten non-diabetic patients were excluded due to lack of urea measurements).

	Adjusted hazard ratio	**95 % CI**	**P value**
Diabetes	2.84	1.35 – 5.99	0.006
Karnofsky equal or less than 80%	4.19	1.86 – 9.46	0.001
Age, years	1.53*	1.00 – 2.34	0.048
Urea, mmol/L	1.78*	1.20 - 2.64	0.004

*Hazard ratio is expressed per quartile

Table 3. Cox multivariate regression analysis with backward directed stepwise procedure about the effect of new postprandial hyperglycaemia on the risk of late death after pneumonia. The included confounders were age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. Only factors with at least suggestive independent association ($p < 0.10$) with the risk of late death are presented. N = 131, only the non-diabetic patients were included.

	Adjusted hazard ratio	**95 % CI**	**P value**
New postprandial hyperglycaemia	2.56	1.04 – 6.32	0.041
Karnofsky equal or less than 80%	3.26	1.12 – 9.47	0.030
Age, years	1.97*	1.14 – 3.39	0.015

*Hazard ratio is expressed per quartile

Table 4. The underlying causes of late death

Group	Cancer	Cardiovascular	Obstructive lung diseases	Miscellaneous
No diabetes, no postprandial hyperglycaemia (9 deaths)	2 (22 %)	4 (44 %)	0 (0 %)	3 (33 %)
No diabetes, with postprandial hyperglycaemia (16 deaths)	1 (6 %)	4 (25 %)	7 (44 %)	4 (25 %)
Diabetes (11 deaths)	3 (27 %)	6 (54 %)	0 (0 %)	2 (18 %)
All patients (36 deaths)	6 (17 %)	14 (39 %)	7 (19 %)	9 (25 %)

DISCUSSION

The present study confirms that both the pre-pneumonia health status and the severity of pneumonia are associated with the late mortality after CAP.[7] Especially, the weight of low functional status was highlighted by the strong association between low Karnofsky score and late mortality. These features were taken into account in the present study. It showed that a pre-pneumonia diagnosis of diabetes is associated with a three-fold increase in the risk of death up to six years after mild to moderate CAP. The study thus corroborates and extends the findings of Yende et al, who reported of increased mortality rates in diabetic patients up to one year after pneumonia.[9] The present study also demonstrated that new postprandial hyperglycaemia among non-diabetic patients shows an independent association with late mortality after pneumonia. Such an association has not been described earlier.

In acute illnesses, complex mechanisms involving hormones and cytokines lead to hyperglycaemia which is mainly caused by excessive hepatic glucose production and manifested by high fasting glucose values.[12] This probably explains our finding that fasting hyperglycaemia was more common than postprandial hyperglycaemia among the non-diabetic CAP patients. As fasting hyperglycaemia was not an independent predictor of mortality in the present study, it may be regarded as an adequate body response to infection. Postprandial hyperglycaemia, in turn, is considered as the first step in the deterioration of glucose homeostasis.[20] In the present study, the survival curves of the diabetic patients and the non-diabetic patients with postprandial hyperglycaemia were almost identical up to 2.5 years. There is evidence suggesting that postprandial hyperglycaemia is an independent risk factor for cardiovascular disease, stroke, retinopathy, renal failure, and neurologic complications in both diabetic and non-diabetic individuals.[20] Excess late mortality after CAP can now be added to that list.

One may suspect that the hyperglycaemic patients without a previous, doctor's diagnosis of diabetes may actually have suffered from diabetes without knowing it. HbA1c reflects mean blood glucose levels during the previous 2 – 3 months and can be used to diagnose diabetes.[21] It is true that the HbA1c values were higher in the non-diabetic patients with new postprandial hyperglycaemia than in those without it. However, the 95 % confidence interval of their HbA1c values was below 6.5 % which is considered diagnostic for diabetes[21] and also well below the HbA1c values of the diabetic patients. In addition, the patients with new postprandial hyperglycaemia did not differ from the euglycaemic non-diabetic patients with respect to family history of diabetes, body mass index, or waist circumference. On the contrary, the patients with a doctor's diagnosis of diabetes clearly differed from the rest of the population by showing all these typical features of type 2 diabetes.[22] Therefore, most of the CAP patients with new postprandial hyperglycaemia probably did not have an undiagnosed diabetes before pneumonia. This supports the view that stress hyperglycaemia and diabetes are two separate disorders.[12 17 23]

The commonly used plasma glucose cut-off values for transient hyperglycaemia during illness (stress hyperglycaemia) have been adopted from the diabetes diagnostics (fasting glucose > 6.9 mmol/l or random glucose > 11.1 mmol/l).[12] To our knowledge, they have not been validated in stress hyperglycaemia. As mentioned, diabetes and stress hyperglycaemia are two separate disorders. The present material gave an opportunity to define plasma glucose cut-off values that best predicted late mortality among the non-diabetic patients: 7.05 mmol/l for fasting glucose and 10.75 mmol/l for postprandial glucose. Our values were surprisingly close to those adopted from diabetes diagnostics and thus support their use also among

non-diabetic patients with stress hyperglycaemia. Utilising the cut-off values from the diabetes diagnostics would not have changed the results of the present study.

The present paper provides some new information how to identify patients at increased risk of death late after CAP. However, it is not known whether the identification of such patients can influence their long-term prognosis. Streptococcus pneumonia vaccination after CAP may be of limited value since just 8 % of all late deaths were caused by pneumonia in the present study. This is in accordance with a larger study in which just 6 % of short-term survivors from CAP finally died of pneumonia.[5] The underlying causes of death in the present population roughly mirrored those in Finnish general population [24] with one exception: In the general population, the proportion of a chronic lung disease as the underlying cause of death is 4 % but in the present population it was 19 %. The above-mentioned Dutch study reported exactly the same finding with much higher numbers of deaths.[5] This may be, at least partly, due to patients with obstructive lung diseases being prone to catch CAP and prone to be hospitalised in case of CAP.[25]

If the possibilities for secondary interventions are to be established, the focus should perhaps be in the primary prevention of pneumonia. The present study suggests that pneumococcus vaccination should be focused on diabetic patients, aged patients, and those with low performance status, among other groups previously reported to show an excessive long-term mortality after pneumonia.[7 26]

The main strength of the present study was the careful way to detect hyperglycaemia during pneumonia with seven plasma glucose measurements during the first day on ward, also including night-time measurements. Most previous studies about the effects of hyperglycaemia on pneumonia prognosis are handicapped by the small number, usually one, of plasma glucose measurements. Plasma glucose levels vary markedly within a day during an acute illness and a single measurement can easily miss the highest values.[17 23] Frequent glucose measurements explain the higher prevalence of new hyperglycaemia in the present study compared with the previous ones.[10 11] The prospective nature and the comprehensive collection of information about possible confounders may also be considered as strengths.

The main limitation of the present study was the lack of validated pneumonia severity scoring. The management of the present patients was based on local guidelines. The Finnish pneumonia guideline suggested the use of a validated severity score not until autumn 2008 [27], i.e., after the present patient

population had been collected. The lack of systematic recording of respiratory rate precludes the calculation of any validated severity scores afterwards. However, many severity-related variables like oxygen saturation, temperature, blood pressure, heart rate, C-reactive protein, leukocytes, urea, and arterial blood gas analysis, were recorded. The population did not include patients who were confused and patients who needed treatment in intensive care unit. The present population thus consists of patients with mild to moderate CAP. Therefore, the results cannot be generalised to all hospitalised pneumonia patients. The relatively small number of patients and deaths may also degrease the generalisibity of the results.

In conclusion, a previous diagnosis of diabetes and newly discovered postprandial hyperglycaemia may increase the risk of death for several years after CAP. As the knowledge about patient subgroups with an increased late mortality risk is gradually gathering, more studies are needed to evaluate the possible post-pneumonia interventions to reduce the late mortality.

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Competing interests

The authors have no competing interests

Ethics approval

The study was reviewed by the Research Ethic Committee, Hospital District of Northern Savo (75//2006) and it was performed in accordance with the ethical standards laid down on the 2000 Declaration of Helsinki. All patients gave their written informed consent.

Contributions

Heikki Koskela has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; He has written the article and is the guarantor.

Päivi Salonen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. She has revised the article critically for important intellectual content and provided final approval of the version to be published.

Jarkko Romppanen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. He has revised the article critically for important intellectual content and provided final approval of the version to be published.

Leo Niskanen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. He has revised the article critically for important intellectual content and provided final approval of the version to be published.

Data sharing statement

Extra data is available by emailing Heikki Koskela

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FIGURE LEGENDS

Figure 1. Inclusion of the patients. Patients were excluded from this study if they had severe pneumonia requiring treatment in the intensive care unit, if they could not give informed consent due to confusion, or if their antibiotic treatment had already been started on another institution.

Figure 2. Kaplan-Meier plot showing long-term survival after community-acquired pneumonia among patients with diabetes (N = 22, the bottom line), non-diabetic patients with new postprandial hyperglycaemia (N = 43, the middle line), and non-diabetic patients without postprandial hyperglycaemia (N = 88, the top line). $P < 0.001$ between the groups.

The long-term mortality after community-acquired pneumonia: Impacts of diabetes and newly discovered hyperglycaemia. A prospective, observational cohort study.

Running title: Pneumonia and hyperglycaemia

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ABSTRACT

Objectives Community-acquired pneumonia is associated with a significant long-term mortality after initial recovery. It has been acknowledged that additional research is urgently needed to examine the contributors to this long-term mortality. The objective of the present study was to assess whether diabetes or newly discovered hyperglycaemia during pneumonia affects the long-term mortality.

Design: A prospective, observational cohort study

Setting: A single secondary centre in eastern Finland

Participants: 153 consecutive hospitalised patients who survived at least 30 days after mild to moderate community-acquired pneumonia.

Interventions: Plasma glucose levels were recorded seven times during the first day on the ward. Several possible confounders were also recorded. The surveillance status and causes of death were recorded after median of five years and eleven months.

Results In multivariate Cox regression analysis, a previous diagnosis of diabetes among the whole population (adjusted hazard ratio 2.84 (1.35 – 5.99)) and new postprandial hyperglycaemia among the non-diabetic population (adjusted hazard ratio 2.56 (1.04 – 6.32)) showed independent associations with late mortality. New fasting hyperglycaemia was not an independent predictor. The mortality rates at the end of follow-up were 54 %, 37 %, and 10 % among patients with diabetes, non-diabetic patients with new postprandial hyperglycaemia, and non-diabetic patients without postprandial hyperglycaemia, respectively ($p < 0.001$). The underlying causes of death roughly mirrored those in Finnish general population with a slight excess in mortality due to chronic respiratory diseases. Pneumonia was the immediate cause of death in just 8 % of all late deaths.

Conclusions A previous diagnosis of diabetes and newly discovered postprandial hyperglycaemia increase the risk of death for several years after community-acquired pneumonia. As the knowledge about patient subgroups with an increased late mortality risk is gradually gathering, more studies are needed to evaluate the possible post-pneumonia interventions to reduce the late mortality.

Strengths and limitations of the study

- The plasma glucose levels were carefully measured during pneumonia 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 is the lack of validated pneumonia severity scoring although several pneumonia severity-related variables were collected
- The present population consists of patients with mild to moderate CAP. Therefore, the results cannot be generalised to all hospitalised pneumonia patients.

INTRODUCTION

Pneumonia is the leading cause of infectious death worldwide with 3.2 million annual casualties.[1] This figure, which is impressive enough *per se*, only contains the acute mortality. Pneumonia is also associated with significant late mortality up to several years afterwards among patients who survive the initial episode. In a large population-based cohort study, the mortality rate was 53 % at five years after an episode of community-acquired pneumonia (CAP).[2] Importantly, the long-term mortality is substantially higher than that of either the general population or a control population hospitalised for reasons other than CAP.[3-5] Given the high and rising incidence of CAP, its long-acting effect on mortality should be regarded as major public health threat.[6 7] It has been acknowledged that additional research is urgently needed to examine the contributors to this long-term mortality.[8]

Probably the most consistently identified contributor to late mortality after CAP is the presence of comorbid conditions, especially neurodegenerative disorders, cardiovascular conditions, malignancy, and chronic obstructive lung disease.[7] To the best of our knowledge, diabetes has not been investigated in this respect. Yende *et al*. analysed two large CAP cohorts and found out that diabetes increased the mortality rate within the first year after CAP with unadjusted hazard ratios (HR) of 1.4 - 1.9.[9] They suggested that the higher mortality may be due to worsening of pre-existing cardiovascular disease or higher risk of acute kidney injury. However, the early and late deaths were not analysed separately and the follow-up time was relatively short.

Hyperglycaemia is associated with short-term mortality in several acute disorders including CAP.[10-14] In pneumonia, a newly detected hyperglycaemia among non-diabetic patients seems to increase the short-term mortality rate more than hyperglycaemia among diabetic patients.[13] The impact of new, pneumonia-associated hyperglycaemia on the long-term mortality has not been investigated. The objective of the present study was to assess whether diabetes or newly discovered hyperglycaemia among non-diabetics affects the late mortality after CAP.

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 CAP were recruited. The patients were considered to have pneumonia if they had an acute febrile illness with a new radiographic shadowing. During that time 245 patients were hospitalised because of pneumonia (figure 1). Patients were excluded from this study if they had severe pneumonia requiring treatment in the intensive care unit, if they could not give informed consent due to confusion, or if their antibiotic treatment had already been started on another institution. Altogether 92 patients were excluded and 153 patients included. All the 153 patients survived at least 30 days after admission. Among them, 22 had a previous diagnosis of diabetes (table 1).

Measurements during pneumonia

During the first 24 hours on the ward the plasma glucose was determined seven times, at three o'clock at night, before breakfast, before lunch, after lunch, before dinner, after dinner, and at bedtime. In addition, the family history for diabetes and the pre-pneumonia Karnofsky performance score were assessed. Karnofsky score is a general measure of patient independence which has most often utilised in patients with cancer.[15 16] Height, weight, waist circumference, oxygen saturation, blood pressure, temperature, and heart rate were measured. Blood tests included glycosylated haemoglobin A1c (HbA1c), N-terminal pro B-type natriuretic peptide (NT-proBNP), C-reactive protein, leukocytes, urea, and arterial blood gas analysis.

The detailed description of the methods and the baseline results have been published.[17] 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 associate with pneumonia prognosis.[18] It was measured from the blood sample collected at admission utilising a commercially available electrochemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). 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.[19]

Table 1. Patient characteristics

	Diabetic patients (N = 22)	p[a]	Patients without diabetes (N = 131)		p[b]	Patients with missing data
			Postprandial hyper-glycaemia (n = 43)	No postprandial hyperglycaemia (n = 88)		
Age, yrs	66 (59 - 73)	0.04	66 (60 - 71)	53 (49 - 58)	0.001	0
Male gender	68 %	0.40	67 %	54 %	0.16	0
Family history of diabetes	68 %	0.004	47 %	30 %	0.07	14
BMI, kg/m2	33 (28 - 37)	0.001	27 (25 - 29)	27 (26 - 29)	0.56	0
Waist circumference, cm	110 (102 - 118)	<0.001	100 (95 - 104)	97 (94 - 100)	0.27	18
gHbA1c, %	7.83 (6.97 - 8.69)	<0.001	6.12 (5.79 - 6.44)	5.64 (5.53 - 5.76)	<0.001	7
Karnofsky 80% or less	50 %	0.02	44 %	16 %	<0.001	0
Three or more comorbidities	54 %	<0.001	23 %	14 %	0.17	0
Diastolic blood pressure, mmHg	75 (69 - 81)	0.12	81 (75 - 86)	80 (77 - 84)	0.99	1
Heart rate, 1/min	99 (90 - 109)	0.22	100 (92 - 107)	91 (86 - 95)	0.005	1
Oxygen saturation (%)	92 (89 - 94)	0.35	91 (89 - 93)	94 (93 - 95)	0.004	13
Leukocytes, 10^9/l	11.8 (9.6 - 13.9)	0.46	12.4 (10.6 - 14.3)	11.7 (10.1 - 13.3)	0.10	0
Urea , mmol/l	6.88 (4.96 - 8.79)	0.28	8.61 (6.41 - 10.8)	4.72 (4.00 - 5.44)	<0.001	11
CRP, mg/l	164 (119 - 209)	0.97	228 (166 - 289)	146 (127 - 165)	<0.001	1
Elevated NT-proBNP	32 %	0.51	29 %	23 %	0.47	4
Length of hospital stay, days	5.8 (4.6 - 7.1)	0.53	6.6 (5.7 - 7.5)	5.9 (5.2 - 6.6)	0.03	1

BMI, body mass index; gHbA1c, glycosylated haemoglobin A1c expressed as percentage of total haemoglobin; CRP, C-reactive protein; NT-proBNP, plasma N-terminal pro B-type natriuretic peptide. The data is presented either as percentage of patients showing the feature or means (95 % confidence intervals)

[a] p value indicates the differences between diabetic and non-diabetic patients

[b] p value indicates the differences between the patients with and without postprandial hyperglycaemia within the non-diabetic patients.

Definitions

Diabetes was defined as doctor's diagnosis of diabetes which had been set before the current pneumonia episode, and verified from the patient files. New hyperglycaemia was defined as hyperglycaemia during the first 24 hours of pneumonia hospitalisation in a patient without a doctor's diagnosis of diabetes. Fasting hyperglycaemia was defined as hyperglycaemia detected at three o'clock at night or at seven o'clock in the morning before breakfast. Postprandial hyperglycaemia was defined as hyperglycaemia detected during the daytime or in the evening. The cut-off values for both fasting and postprandial hyperglycaemia among the non-diabetic patients were those defined by the receiver operator curves (ROC) analysis (see below). The main outcome variable was mortality from 30 days after pneumonia up to the end of follow-up. The predictor variables were diabetes, new fasting hyperglycaemia, and new postprandial hyperglycaemia. A confounder was a variable which showed an association with both the plasma glucose levels during pneumonia and the late mortality. However, a potential confounder with a causal relationship to the outcome variable was not included. Furthermore, if two potential confounders were closely interrelated, the one with a closer association with the plasma glucose levels was included.

Follow-up after pneumonia

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 version 10, were obtained from death certificates. The median follow-up was five years and eleven months.

Ethics

The study was reviewed by the Research Ethic Committee, Hospital District of Northern Savo (75//2006) and it was performed in accordance with the ethical standards laid down on the 2000 Declaration of Helsinki. All patients gave their written informed consent.

Statistical analysis

Comparative survival curves were constructed using Kaplan-Meier methodology. The unadjusted HRs were assessed utilising univariate Cox regression analysis. Continuous data was divided to quartiles. The assumption of proportional hazard was checked by graphically comparing the hazard curves. To determinate the adjusted HRs for diabetes, new fasting hyperglycaemia and new postprandial hyperglycaemia, Cox multivariate regression analysis with backwards directed stepwise procedure was utilised. In this analysis patients with missing data were excluded.

The analysis about the effect of new hyperglycaemia was restricted to the 131 non-diabetic pneumonia patients. Among them, ROC curves were produced for both fasting and postprandial plasma glucose values to define the best cut-off values to predict death during the follow-up.

Frequency comparison was performed by Chi-squared test. Student's T-test and Pearson correlation coefficient were utilised when appropriate. Categorical data is expressed as percentages and continuous data as means and 95 % confidence intervals (CI). 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

Univariate analysis and the ROC analysis

Table 1 shows the numbers of patients in each subgroup and their characteristics. The following features showed a statistically significant association with the late mortality within the whole population: Presence of diabetes (HR 3.5 (1.7 - 6.9), figure 2), advanced age, Karnofsky score equal or less than 80 %, presence of three or more co-morbidities, low diastolic blood pressure, low arterial blood oxygen saturation, high urea,

NT-proBNP above predicted value[19], high gHbA1c, and long hospital stay (data not shown). The proportional hazards remained constant over time.

Among the non-diabetic patients, the ROC analysis of the fasting plasma glucose measurements revealed that the level of 7.05 mmol/l was the best cut-off value to predict late mortality (results not shown). A glucose level exceeding it showed an unadjusted HR of 2.7 (1.1 – 6.4) (p = 0.027). 52 % of the non-diabetic patients showed a fasting glucose level exceeding 7.05 mmol/l. In one patient, no fasting glucose values were obtained. The ROC analysis of the postprandial glucose measurements revealed that the level of 10.75 mmol/l was the best cut-off value (results not shown). The corresponding unadjusted HR was 4.2 (1.9 – 9.6) (p = 0.001, figure 2). 33 % of the non-diabetic patients showed a postprandial glucose level exceeding 10.75 mmol/l. Utilising these plasma glucose cut-off values among the 22 diabetic patients it could be shown that 19 of them (86 %) showed fasting hyperglycaemia and 18 (82 %) showed postprandial hyperglycaemia.

Multivariate analysis

The following confounders were included: Age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. The results of the multivariate Cox regression analysis are shown in tables 2 and 3. It can be seen that a diagnosis of diabetes among the whole population (table 2) and new postprandial hyperglycaemia among the non-diabetic population (table 3) showed independent associations with late mortality after pneumonia. New fasting hyperglycaemia was not a predictor of mortality when the confounders were taken into account (p = 0.74).

The mortality rates and the causes of death

The mortality rates at the end of follow-up were 54 %, 37 %, and 10 % among patients with diabetes, non-diabetic patients with new postprandial hyperglycaemia, and non-diabetic patients without postprandial hyperglycaemia, respectively (p < 0.001). The underlying causes of death are shown in table 4. The immediate causes of death mirrored the underlying causes. Pneumonia was the immediate cause of death in just three cases (8 % of all deaths).

Table 2. Cox multivariate regression analysis with backward directed stepwise procedure about the effect of diabetes on the risk of late death after pneumonia. The included confounders were age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. Only factors with at least suggestive independent association ($p < 0.10$) with the risk of late death are presented. N = 142 (one diabetic and ten non-diabetic patients were excluded due to lack of urea measurements).

	Adjusted hazard ratio	**95 % CI**	**P value**
Diabetes	2.84	1.35 – 5.99	0.006
Karnofsky equal or less than 80%	4.19	1.86 – 9.46	0.001
Age, years	1.53*	1.00 – 2.34	0.048
Urea, mmol/L	1.78*	1.20 - 2.64	0.004

*Hazard ratio is expressed per quartile

Table 3. Cox multivariate regression analysis with backward directed stepwise procedure about the effect of new postprandial hyperglycaemia on the risk of late death after pneumonia. The included confounders were age, Karnofsky score equal or less than 80%, elevated plasma NT-proBNP, and plasma urea concentration. Only factors with at least suggestive independent association ($p < 0.10$) with the risk of late death are presented. N = 131, only the non-diabetic patients were included.

	Adjusted hazard ratio	**95 % CI**	**P value**
New postprandial hyperglycaemia	2.56	1.04 – 6.32	0.041
Karnofsky equal or less than 80%	3.26	1.12 – 9.47	0.030
Age, years	1.97*	1.14 – 3.39	0.015

*Hazard ratio is expressed per quartile

Table 4. The underlying causes of late death

Group	Cancer	Cardiovascular	Obstructive lung diseases	Miscellaneous
No diabetes, no postprandial hyperglycaemia (9 deaths)	2 (22 %)	4 (44 %)	0 (0 %)	3 (33 %)
No diabetes, with postprandial hyperglycaemia (16 deaths)	1 (6 %)	4 (25 %)	7 (44 %)	4 (25 %)
Diabetes (11 deaths)	3 (27 %)	6 (54 %)	0 (0 %)	2 (18 %)
All patients (36 deaths)	6 (17 %)	14 (39 %)	7 (19 %)	9 (25 %)

DISCUSSION

The present study confirms that both the pre-pneumonia health status and the severity of pneumonia are associated with the late mortality after CAP.[7] Especially, the weight of low functional status was highlighted by the strong association between low Karnofsky score and late mortality. These features were taken into account in the present study. It showed that a pre-pneumonia diagnosis of diabetes is associated with a three-fold increase in the risk of death up to six years after mild to moderate CAP. The study thus corroborates and extends the findings of Yende et al, who reported of increased mortality rates in diabetic patients up to one year after pneumonia.[9] The present study also demonstrated that new postprandial hyperglycaemia among non-diabetic patients shows an independent association with late mortality after pneumonia. Such an association has not been described earlier.

In acute illnesses, complex mechanisms involving hormones and cytokines lead to hyperglycaemia which is mainly caused by excessive hepatic glucose production and manifested by high fasting glucose values.[12] This probably explains our finding that fasting hyperglycaemia was more common than postprandial hyperglycaemia among the non-diabetic CAP patients. As fasting hyperglycaemia was not an independent predictor of mortality in the present study, it may be regarded as an adequate body response to infection. Postprandial hyperglycaemia, in turn, is considered as the first step in the deterioration of glucose homeostasis.[20] In the present study, the survival curves of the diabetic patients and the non-diabetic patients with postprandial hyperglycaemia were almost identical up to 2.5 years. There is evidence suggesting that postprandial hyperglycaemia is an independent risk factor for cardiovascular disease, stroke, retinopathy, renal failure, and neurologic complications in both diabetic and non-diabetic individuals.[20] Excess late mortality after CAP can now be added to that list.

One may suspect that the hyperglycaemic patients without a previous, doctor's diagnosis of diabetes may actually have suffered from diabetes without knowing it. HbA1c reflects mean blood glucose levels during the previous 2 – 3 months and can be used to diagnose diabetes.[21] It is true that the HbA1c values were higher in the non-diabetic patients with new postprandial hyperglycaemia than in those without it. However, the 95 % confidence interval of their HbA1c values was below 6.5 % which is considered diagnostic for diabetes[21] and also well below the HbA1c values of the diabetic patients. In addition, the patients with new postprandial hyperglycaemia did not differ from the euglycaemic non-diabetic patients with respect to family history of diabetes, body mass index, or waist circumference. On the contrary, the patients with a doctor's diagnosis of diabetes clearly differed from the rest of the population by showing all these typical features of type 2 diabetes.[22] Therefore, most of the CAP patients with new postprandial hyperglycaemia probably did not have an undiagnosed diabetes before pneumonia. This supports the view that stress hyperglycaemia and diabetes are two separate disorders.[12 17 23]

The commonly used plasma glucose cut-off values for transient hyperglycaemia during illness (stress hyperglycaemia) have been adopted from the diabetes diagnostics (fasting glucose > 6.9 mmol/l or random glucose > 11.1 mmol/l).[12] To our knowledge, they have not been validated in stress hyperglycaemia. As mentioned, diabetes and stress hyperglycaemia are two separate disorders. The present material gave an opportunity to define plasma glucose cut-off values that best predicted late mortality among the non-diabetic patients: 7.05 mmol/l for fasting glucose and 10.75 mmol/l for postprandial glucose. Our values were surprisingly close to those adopted from diabetes diagnostics and thus support their use also among

non-diabetic patients with stress hyperglycaemia. Utilising the cut-off values from the diabetes diagnostics would not have changed the results of the present study.

The present paper provides some new information how to identify patients at increased risk of death late after CAP. However, it is not known whether the identification of such patients can influence their long-term prognosis. Streptococcus pneumonia vaccination after CAP may be of limited value since just 8 % of all late deaths were caused by pneumonia in the present study. This is in accordance with a larger study in which just 6 % of short-term survivors from CAP finally died of pneumonia.[5] The underlying causes of death in the present population roughly mirrored those in Finnish general population [24] with one exception: In the general population, the proportion of a chronic lung disease as the underlying cause of death is 4 % but in the present population it was 19 %. The above-mentioned Dutch study reported exactly the same finding with much higher numbers of deaths.[5] This may be, at least partly, due to patients with obstructive lung diseases being prone to catch CAP and prone to be hospitalised in case of CAP.[25]

If the possibilities for secondary interventions are to be established, the focus should perhaps be in the primary prevention of pneumonia. The present study suggests that pneumococcus vaccination should be focused on diabetic patients, aged patients, and those with low performance status, among other groups previously reported to show an excessive long-term mortality after pneumonia.[7 26]

The main strength of the present study was the careful way to detect hyperglycaemia during pneumonia with seven plasma glucose measurements during the first day on ward, also including night-time measurements. Most previous studies about the effects of hyperglycaemia on pneumonia prognosis are handicapped by the small number, usually one, of plasma glucose measurements. Plasma glucose levels vary markedly within a day during an acute illness and a single measurement can easily miss the highest values.[17 23] Frequent glucose measurements explain the higher prevalence of new hyperglycaemia in the present study compared with the previous ones.[10 11] The prospective nature and the comprehensive collection of information about possible confounders may also be considered as strengths.

The main limitation of the present study was the lack of validated pneumonia severity scoring. The management of the present patients was based on local guidelines. The Finnish pneumonia guideline suggested the use of a validated severity score not until autumn 2008 [27], i.e., after the present patient

population had been collected. The lack of systematic recording of respiratory rate precludes the calculation of any validated severity scores afterwards. However, many severity-related variables like oxygen saturation, temperature, blood pressure, heart rate, C-reactive protein, leukocytes, urea, and arterial blood gas analysis, were recorded. The population did not include patients who were confused and patients who needed treatment in intensive care unit. The present population thus consists of patients with mild to moderate CAP. Therefore, the results cannot be generalised to all hospitalised pneumonia patients. The relatively small number of patients and deaths may also degrease the generalisibity of the results.

In conclusion, a previous diagnosis of diabetes and newly discovered postprandial hyperglycaemia may increase the risk of death for several years after CAP. As the knowledge about patient subgroups with an increased late mortality risk is gradually gathering, more studies are needed to evaluate the possible post-pneumonia interventions to reduce the late mortality.

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Competing interests

The authors have no competing interests

Ethics approval

The study was reviewed by the Research Ethic Committee, Hospital District of Northern Savo (75//2006) and it was performed in accordance with the ethical standards laid down on the 2000 Declaration of Helsinki. All patients gave their written informed consent.

Contributions

Heikki Koskela has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data; He has written the article and is the guarantor.

Päivi Salonen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. She has revised the article critically for important intellectual content and provided final approval of the version to be published.

Jarkko Romppanen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. He has revised the article critically for important intellectual content and provided final approval of the version to be published.

Leo Niskanen has made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data. He has revised the article critically for important intellectual content and provided final approval of the version to be published.

Data sharing statement

Extra data is available by emailing Heikki Koskela

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FIGURE LEGENDS

Figure 1. Inclusion of the patients. Patients were excluded from this study if they had severe pneumonia requiring treatment in the intensive care unit, if they could not give informed consent due to confusion, or if their antibiotic treatment had already been started on another institution.

Figure 2. Kaplan-Meier plot showing long-term survival after community-acquired pneumonia among patients with diabetes (N = 22, the bottom line), non-diabetic patients with new postprandial hyperglycaemia (N = 43, the middle line), and non-diabetic patients without postprandial hyperglycaemia (N = 88, the top line). $P < 0.001$ between the groups.

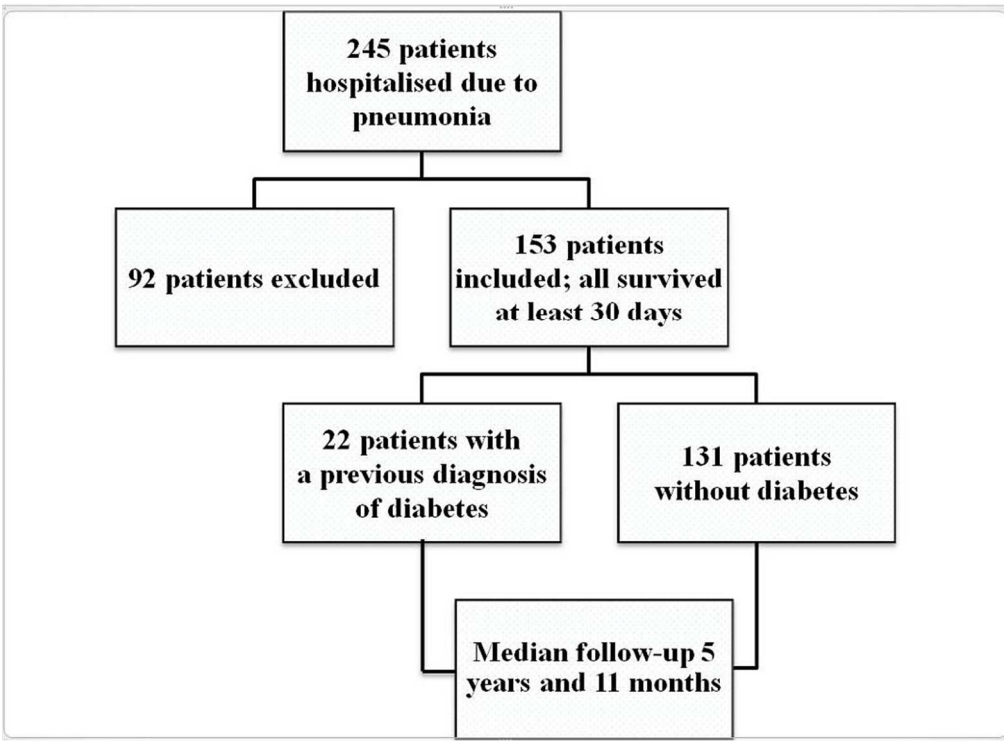

Figure 1
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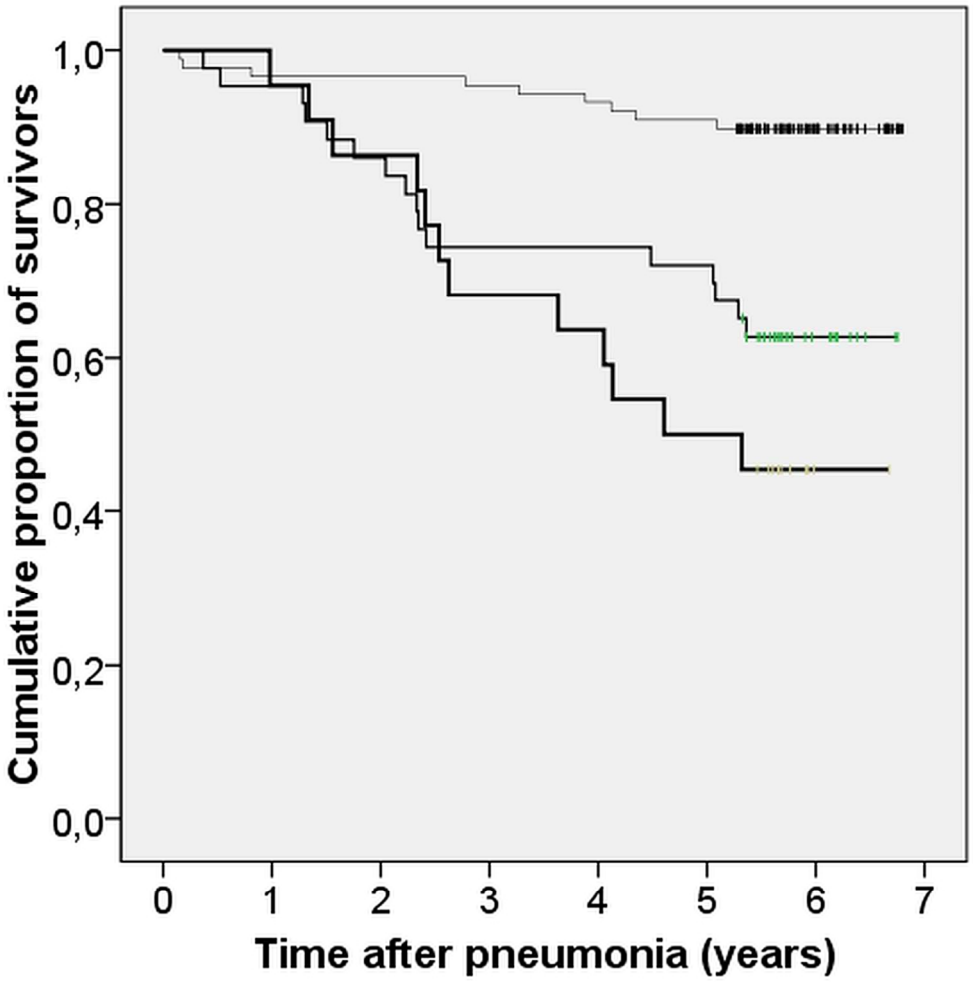

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	*(a)* Indicate the study's design with a commonly used term in the title or the abstract PAGES 1, 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found PAGE 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported PAGE 4
Objectives	3	State specific objectives, including any prespecified hypotheses PAGE 4
Methods		
Study design	4	Present key elements of study design early in the paper PAGE 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection PAGE 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up PAGE 5 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable PAGE 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group PAGE 5
Bias	9	Describe any efforts to address potential sources of bias PAGES 13,14
Study size	10	Explain how the study size was arrived at PAGE 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why PAGES 7, 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding PAGES 7,8
		(*b*) Describe any methods used to examine subgroups and interactions PAGES 7,9
		(*c*) Explain how missing data were addressed PAGE 8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed NO LOSS TO FOLLOW-UP *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses PAGE 8

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed PAGE 5
		(b) Give reasons for non-participation at each stage PAGE 5
		(c) Consider use of a flow diagram FIGURE 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders TABLE 1
		(b) Indicate number of participants with missing data for each variable of interest TABLE 1
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) PAGE 7
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time PAGE 7
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included PAGES 8,9, TABLES 2, 3
		(*b*) Report category boundaries when continuous variables were categorized PAGE 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period PAGE 9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses PAGE 10
Discussion		
Key results	18	Summarise key results with reference to study objectives PAGE 11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias PAGES 13,14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence PAGE 14
Generalisability	21	Discuss the generalisability (external validity) of the study results PAGES 13, 14
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based PAGE 15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.