

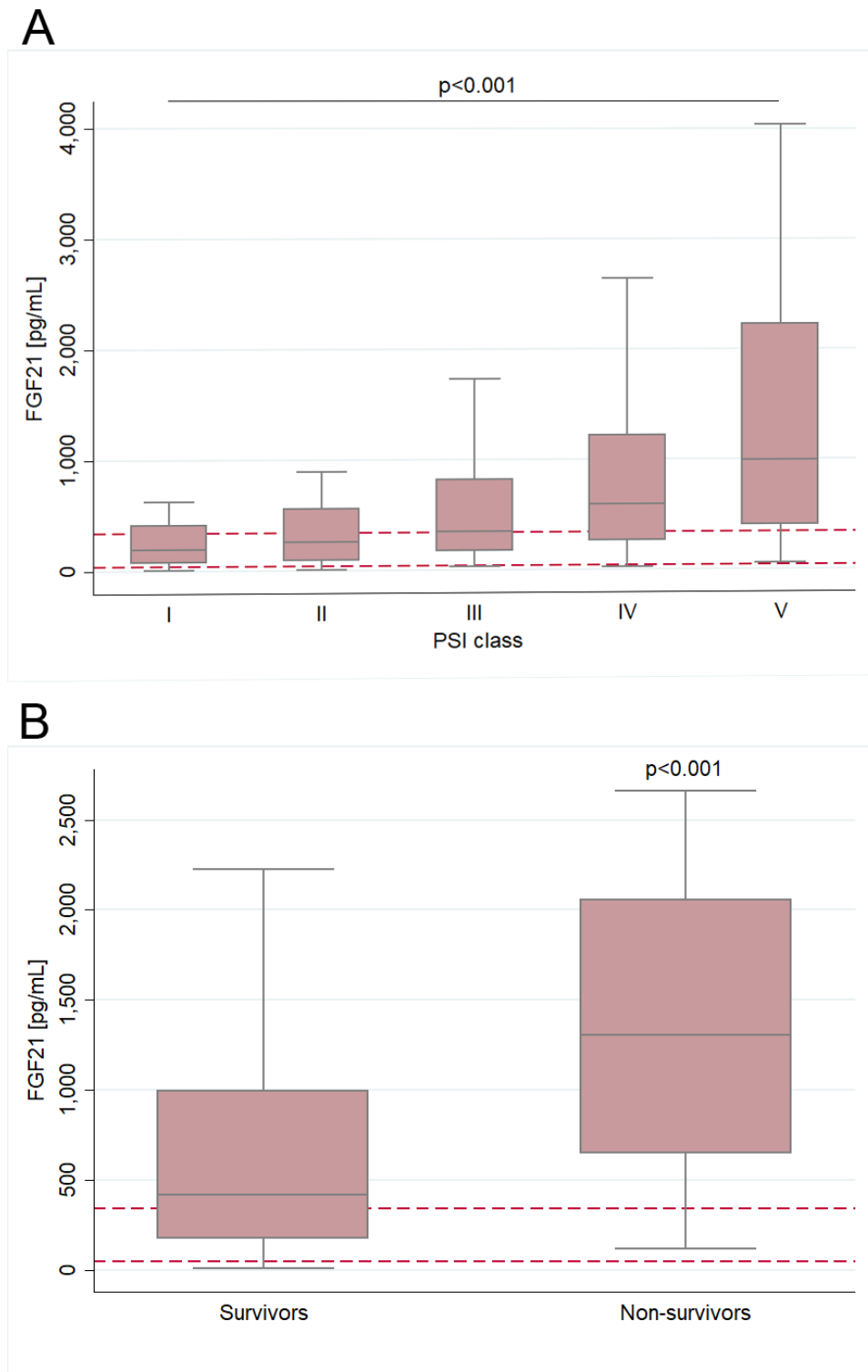
Online Supplemental Material

Fibroblast Growth Factor-21 Predicts Outcome in Community-Acquired Pneumonia

Contents

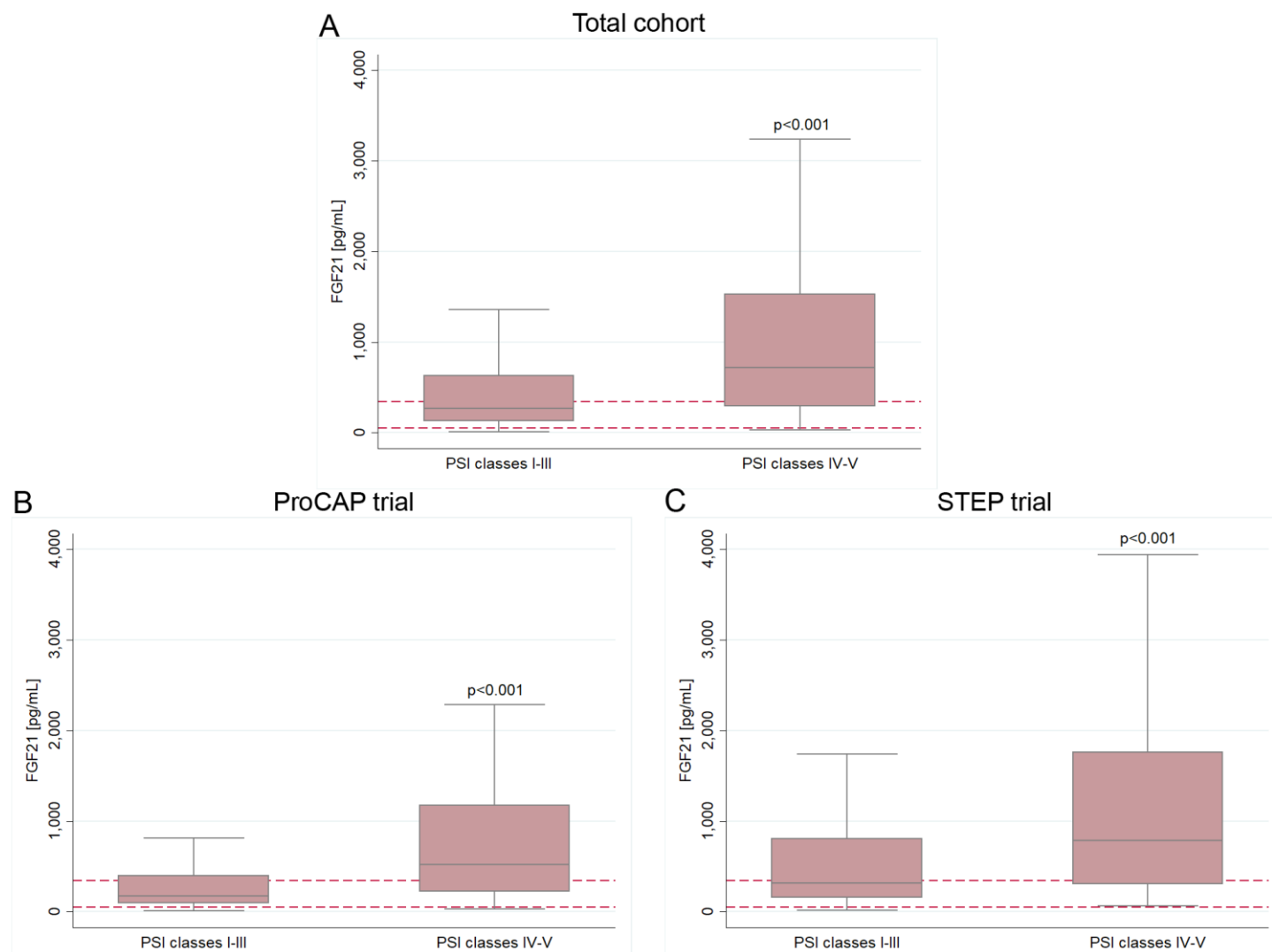
1. Figure S1. FGF21 levels and clinical outcomes	2
2. Figure S2. FGF21 and Pneumonia Severity Index at Emergency Admission.....	3
3. Figure S3. FGF21 and Procalcitonin at Emergency Admission.....	4
4. Figure S4. FGF21 and C-reactive protein at Emergency Admission	5
5. Figure S5. FGF21 and Body Temperature at Emergency Admission.....	6
6. Figure S6. FGF21 and Pneumonia Severity Index (PSI)	7
7. Figure S7. Effects of Corticosteroids on FGF21 levels	8
8. Figure S8. FGF21 and Glucose levels at Emergency Admission	9
9. Table S1. Baseline characteristics of the ProCAP and STEP cohorts.....	10
10. Table S2a. Baseline characteristics of young healthy volunteers.....	11
11. Table S2b. Baseline characteristics of older healthy volunteers.....	11
12. Table S3. FGF21 and Pneumonia severity index to predict 30-day mortality: Sensitivity, Specificity, Positive likelihood ratio, and negative likelihood ratio at various cutoff values	12
13. Table S4. Diagnostic accuracy to discriminate among low-risk (PSI I-III) versus high-risk (PSI IV-V) in community-acquired pneumonia	12
14. Table S5. FGF21 and clinical outcomes in STEP trial	13
15. Table S6. FGF21 clinical outcomes in ProCAP trial	14
16. References	15

1. Figure S1. FGF21 levels and clinical outcomes



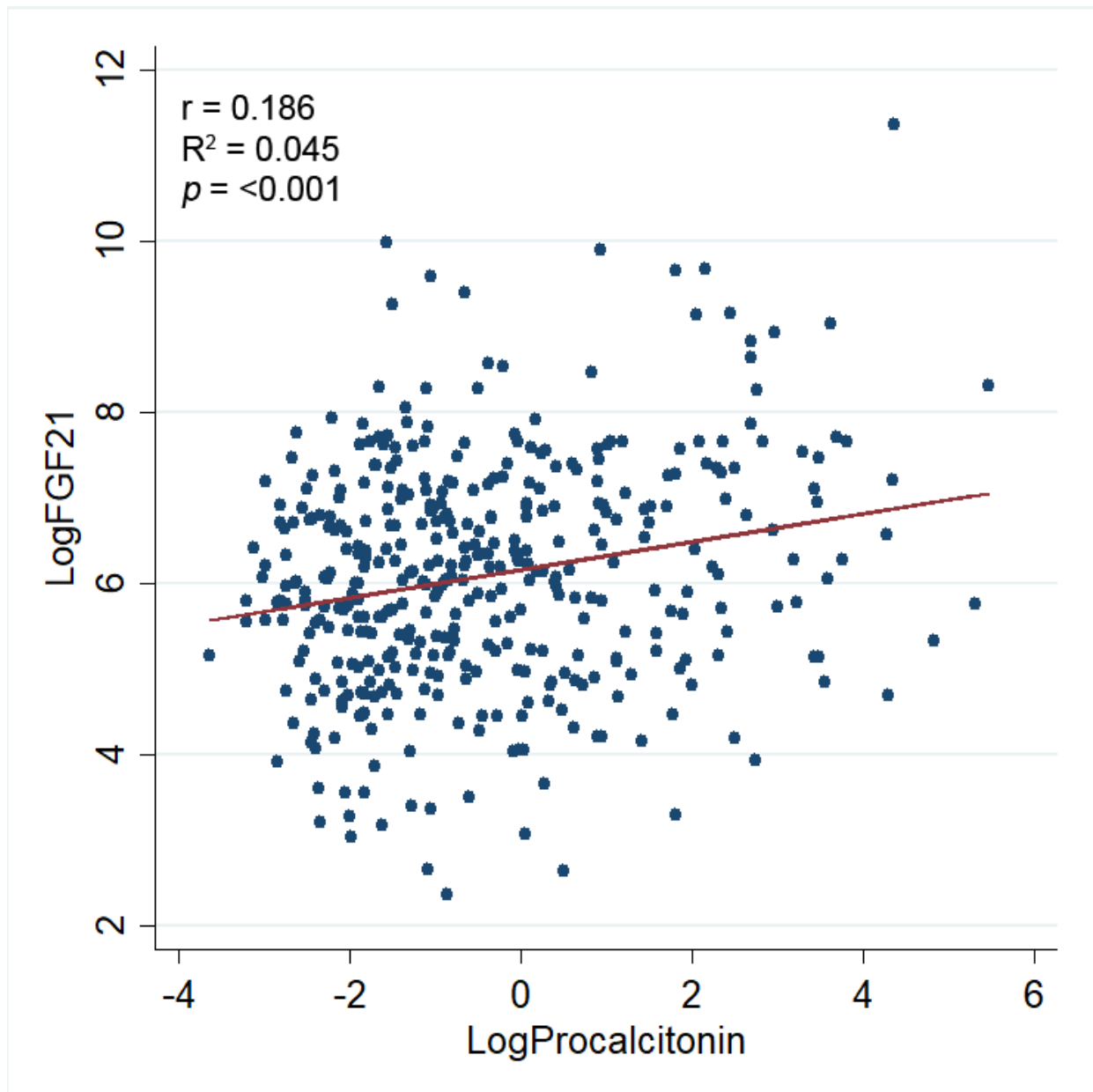
Boxplots for levels of FGF21 at baseline stratified by PSI classes (A) and between Survivors and Non-Survivors (B) for the combined population of ProCAP trial cohort and STEP trial cohort..

2. Figure S2. FGF21 and Pneumonia Severity Index at Emergency Admission



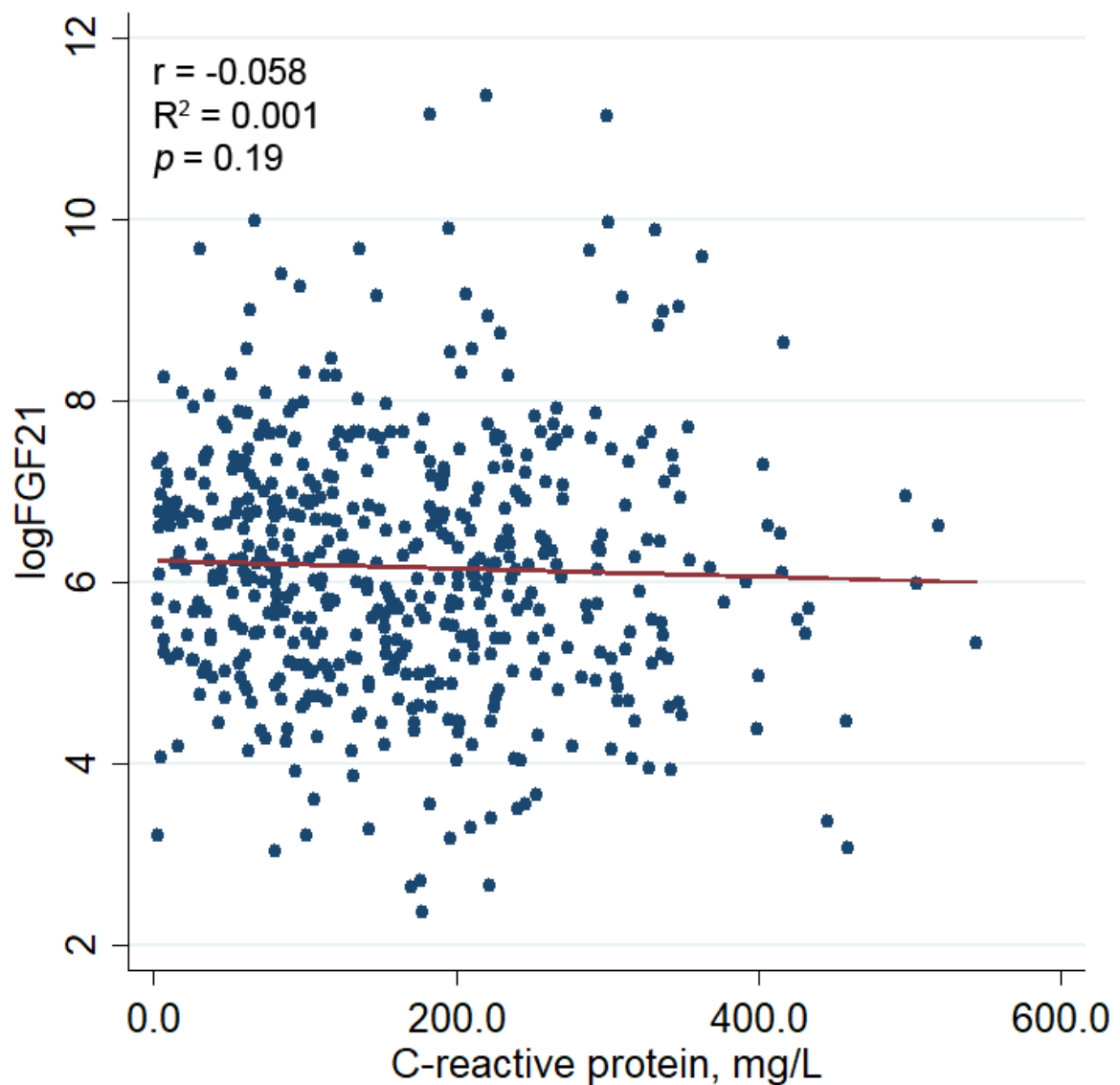
Boxplots for levels of FGF21 at baseline stratified by PSI classes I-III (low-risk) versus PSI classes IV-V (high-risk) for the pooled cohort (A), for the ProCAP trial (B) and for the STEP trial cohort (C).

3. Figure S3. FGF21 and Procalcitonin at Emergency Admission



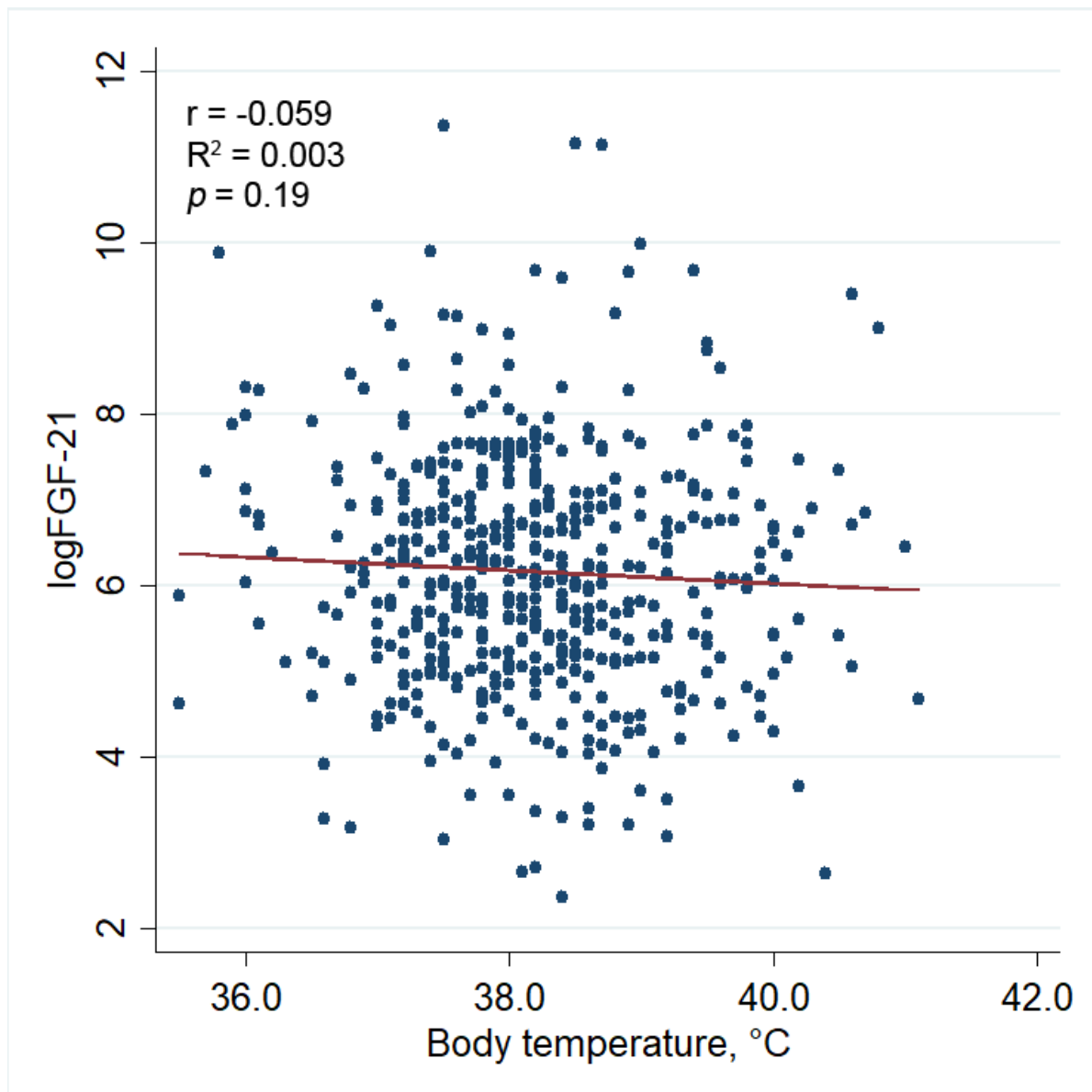
Scatter plot with fitted linear regression line for baseline levels of log-transformed Fibroblast Growth Factor-21 (FGF21) and log-transformed procalcitonin levels at emergency admission. There is a significant correlation between these two inflammatory parameters ($r=0.186$, R^2 0.045; $p<0.001$).

4. Figure S4. FGF21 and C-reactive protein at Emergency Admission



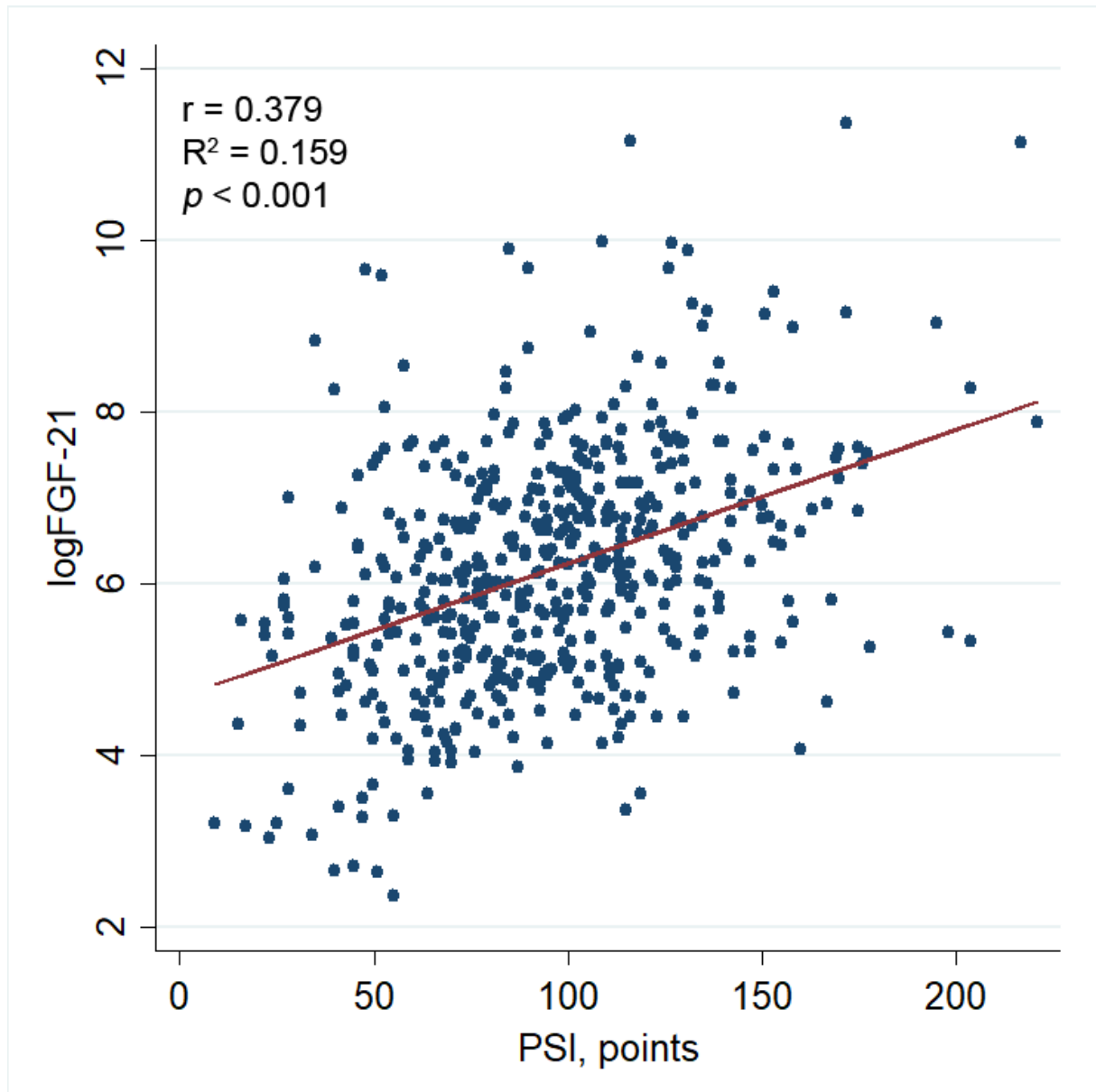
Scatter plot with fitted linear regression line for baseline levels of log-transformed Fibroblast Growth Factor-21 (FGF21) and c-reactive protein levels at emergency admission. There is no significant correlation between these parameters.

5. Figure S5. FGF21 and Body Temperature at Emergency Admission



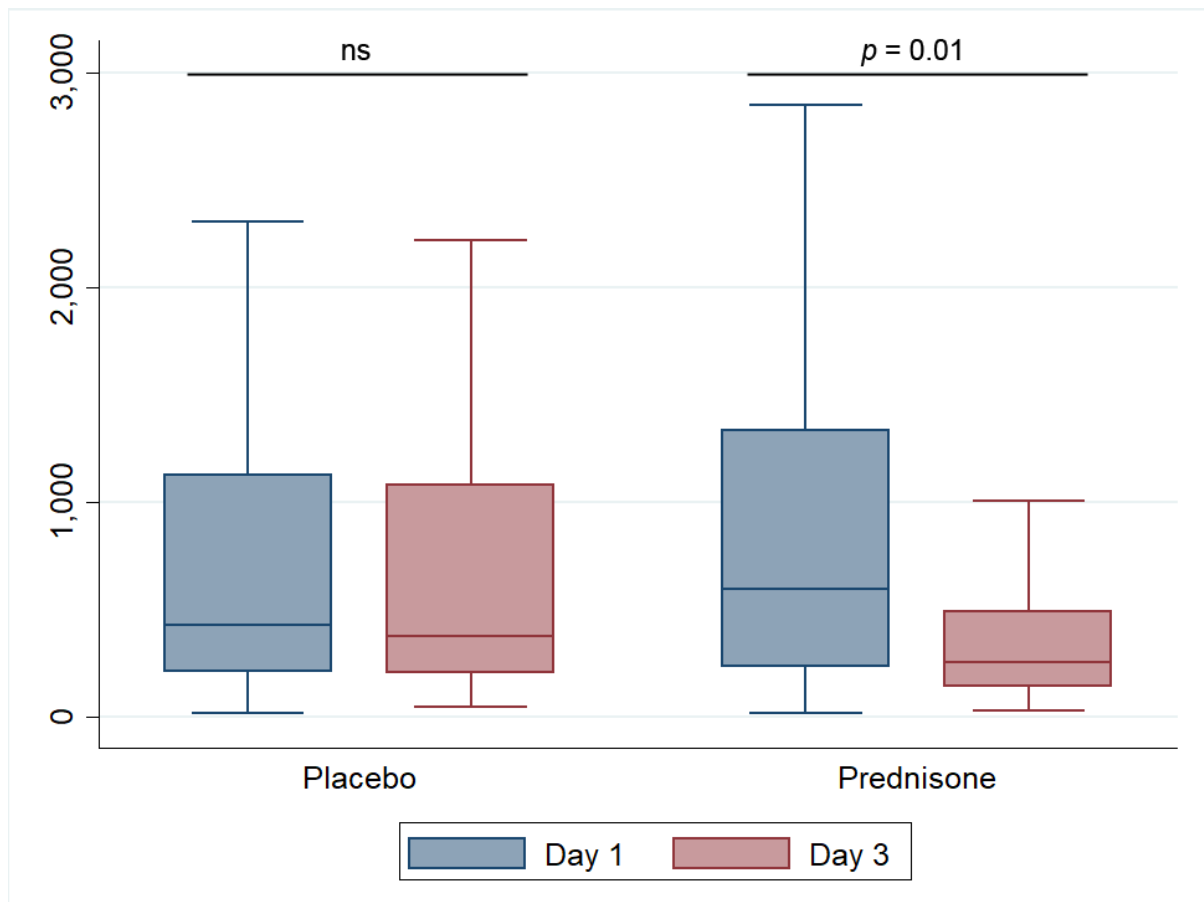
Scatter plot with fitted linear regression line for baseline levels of log-transformed Fibroblast Growth Factor-21 (FGF21) and body temperature at emergency admission. There is no significant correlation between these parameters.

6. Figure S6. FGF21 and Pneumonia Severity Index (PSI)



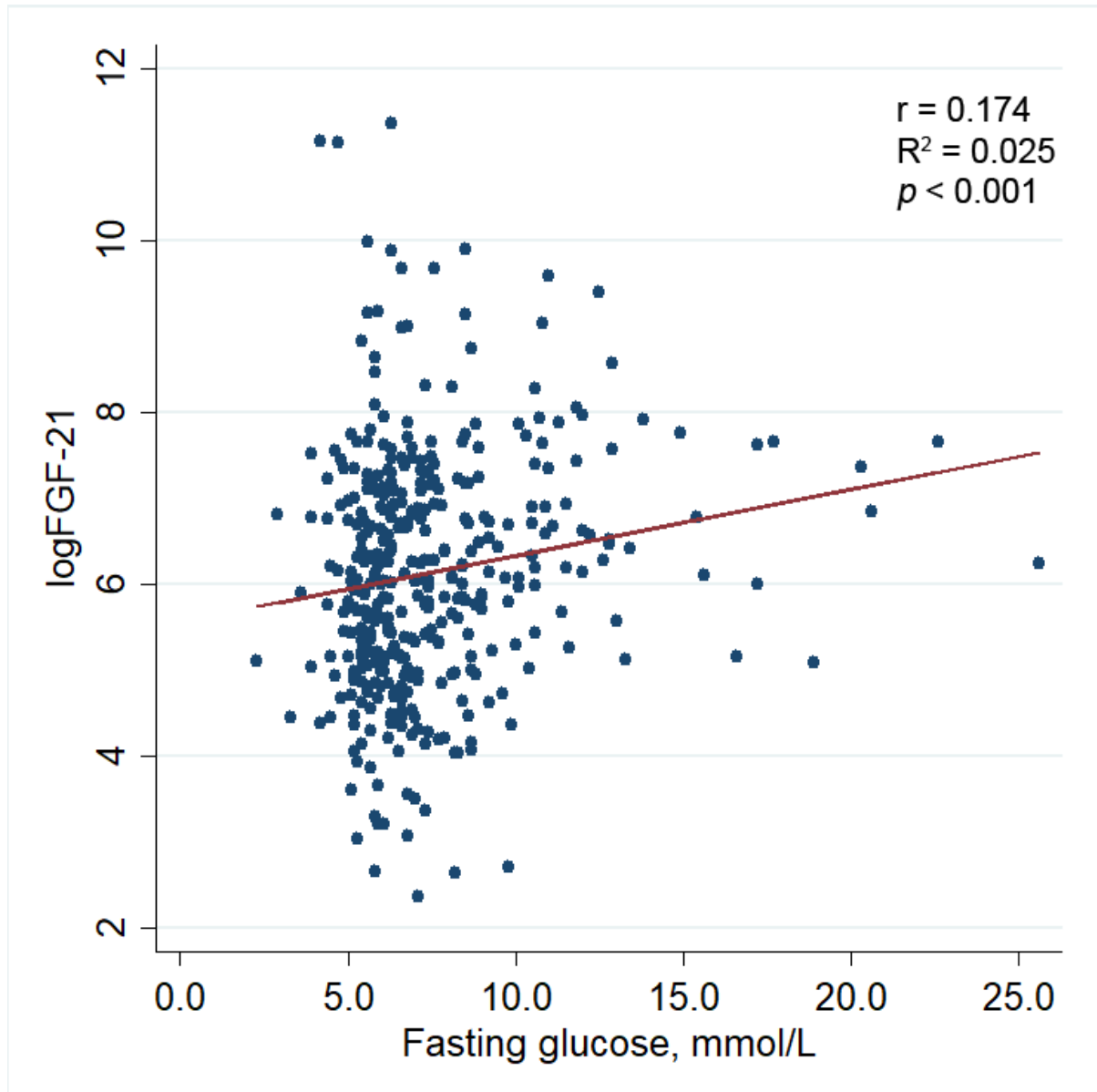
Scatter plot with fitted linear regression line for baseline levels of log-transformed Fibroblast Growth Factor-21 (FGF21) and Pneumonia Severity Index (PSI) of the pooled total cohort (ProCAP and STEP trials), revealing a significant positive correlation of FGF21 with disease severity.

7. Figure S7. Effects of Corticosteroids on FGF21 levels



Box plots for levels of Fibroblast Growth Factor-21 (FGF21 in pg/mL) at emergency admission (blue) and day 3 (red) stratified by randomized treatment (Placebo vs. Prednisone). There was a significant decrease in FGF21 levels at day 3 upon treatment with prednisone 50mg per day.

8. Figure S8. FGF21 and Glucose levels at Emergency Admission



Scatter plot with fitted linear regression line for baseline levels of log-transformed Fibroblast Growth Factor-21 (FGF21) and glucose levels at emergency admission of the pooled total cohort (ProCAP and STEP trials), revealing a significant positive correlation of FGF21 with plasma glucose.

9. Table S1. Baseline characteristics of the ProCAP and STEP cohorts

Characteristic/variable	Total cohort (n=509)	ProCAP trial (n=150)	STEP trial (n=359)
General characteristics			
Age, years	75 (61, 83)	73.0 (56.0, 82.0)	75 (62, 83)
Male sex	320 (62.9%)	93 (62.0%)	227 (63.2%)
BMI, kg/m ²	26.0 (23.0, 29.3)	24.8 (22.2, 28.7)	26.1 (23.0, 29.4)
Smoking status	118 (23.2%)	32 (21.3%)	86 (24.0%)
Packyears, years	20.0 (0.0, 40.0)	30.0 (20.0, 50.0)	10.0 (0.0, 40.0)
Comorbidities			
Diabetes mellitus	117 (23.0%)	35 (23.3%)	82 (22.8%)
COPD	100 (19.6%)	32 (21.3%)	68 (18.9%)
Asthma	21 (4.1%)	3 (2.0%)	18 (5.0%)
Heart failure	83 (16.3%)	9 (6.0%)	74 (20.6%)
Cerebrovascular disease	44 (8.6%)	9 (6.0%)	35 (9.7%)
Renal insufficiency	165 (32.4%)	34 (22.7%)	131 (36.5%)
Neoplastic disease	41 (8.1%)	23 (15.3%)	18 (5.0%)
Antibiotic pre-treatment	109 (21.4%)	31 (20.7%)	78 (21.7%)
Clinical variables			
Systolic blood pressure, mmHg	125.0 (110.0, 140.0)	130.0 (113.0, 142.0)	124.0 (110.0, 140.0)
Heart rate, bpm	88.0 (76.0, 101.0)	96.0 (84.0, 108.0)	85.0 (74.0, 98.0)
Respiratory rate, breaths/min	21.0 (18.0, 25.0)	22.0 (18.0, 27.0)	20.0 (18.0, 24.0)
Body temperature, °C [in-ear]	38.1 (37.5, 38.7)	38.5 (37.7, 39.3)	38.0 (37.4, 38.6)
SIRS, points.	2 (2, 3)	3 (2, 4)	2 (2, 3)
PSI class [†]			
I, II and III	227 (44.6%)	64 (42.7%)	163 (45.4%)
IV and V	282 (55.4%)	86 (57.3%)	196 (54.6%)
PSI, points [†]	95 (71, 118)	95 (71, 115)	95 (71, 118)
Laboratory values			
C-reactive protein, mg/L	153.0 (80.0, 233.0)	135.5 (74.0, 216.4)	153.6 (80.1, 240.0)
Procalcitonin, ng/dL	0.4 (0.2, 1.9)	0.4 (0.2, 1.4)	0.4 (0.2, 2.5)
White blood cell count, G/L	12.2 (8.8, 15.4)	12.8 (9.0, 15.4)	12.0 (8.7, 15.4)
Fasting glucose, mmol/L	6.6 (5.7, 8.4)	6.8 (5.8, 8.7)	6.6 (5.7, 7.8)

Data are presented as median (interquartile range) or n (%), unless otherwise stated. BMI: body mass index; COPD: chronic obstructive pulmonary disease; SIRS: systemic inflammatory response syndrome; PSI: Pneumonia Severity Index. [†] The PSI is a clinical prediction rule to calculate the probability of morbidity and mortality in patients with community-acquired pneumonia [1]; PSI risk class I corresponds to age ≤50 years and no risk factors (≤50 points), risk class II to 51–70 points, risk class III to 71–90 points, risk class IV to 91–130 points and risk class V to >130 points.

10. Table S2a. Baseline characteristics of young healthy volunteers

Characteristic/variable		Total cohort (n=56)
Sex	Female	11 (20%)
	Male	45 (80%)
Age, years		24 (22, 29.5)
Weight, kg		74.5 (68.5, 79.1)
Height, cm		179.5 (173, 183)
BMI, kg/m ²		23.1 (21.5, 24.7)
FGF21, pg/mL		50.4 (13.7, 113.3)

Data are presented as median (IQR) for continuous or n (%) for categorical variables. BMI, body mass index.

11. Table S2b. Baseline characteristics of older healthy volunteers

Characteristic/variable		Total cohort (n=56)
Sex	Female	28 (70%)
	Male	12 (30%)
Age, years		64 (59.5, 71.5)
Weight, kg		64.5 (57.5, 78.1)
Height, cm		166 (160, 169)
BMI, kg/m ²		23.4 (21.3, 26.2)
C-reactive protein, mg/L		1.0 (0.4, 1.6)
FGF21, pg/mL		140.2 (81.1, 161.8)

Data are presented as median (IQR) for continuous or n (%) for categorical variables. BMI, body mass index.

12. Table S3. FGF21 and Pneumonia severity index to predict 30-day mortality: Sensitivity, Specificity, Positive likelihood ratio, and negative likelihood ratio at various cutoff values

Cutoff	Sensitivity	Specificity	LR+	LR-
FGF21				
386	90.6	46.8	1.7	0.2
669	75.0	62.7	2.0	0.4
1933	31.3	86.6	2.3	0.8
PSI				
95	90.6	52.4	1.9	0.2
102	84.4	60.6	2.1	0.3
134	31.3	87.6	2.5	0.8

Definition of abbreviations: FGF21 = Fibroblast growth factor-21; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; PSI = pneumonia severity index.

13. Table S4. Diagnostic accuracy to discriminate among low-risk (PSI I-III) versus high-risk (PSI IV-V) in community-acquired pneumonia

Parameter	AUC	95% CI	p Value (vs. FGF21)
FGF21	0.68	0.64–0.73	–
C-reactive Protein	0.48	0.43–0.53	<0.001
Procalcitonin	0.56	0.51–0.62	0.02
White blood cell count	0.46	0.41–0.51	<0.001

Definition of abbreviations: AUC = area under the curve; CI = confidence interval; FGF21 = Fibroblast growth factor-21; PSI = pneumonia severity index.

14. Table S5. FGF21 and clinical outcomes in STEP trial

			Regression Analysis of Baseline FGF21			
	<u>Tertiles 1-2</u> n=240	<u>Tertile 3</u> n=119	Univariate regression analysis, OR, HR, coefficient (95% CI)	<i>p</i> value	Multivariable adjusted regression analysis, OR, HR, coefficient (95% CI)	<i>p</i> value
Death (30-days)	5 (2.1%)	10 (8.4%)	1.53 (1.09, 2.14)	0.01	1.53 (0.99, 2.36)	0.05
Time to effective hospital discharge, days	7.0 (6.0-8.0)	10.0 (8.0-11.0)	0.85 (0.78, 0.92)	<0.001	0.87 (0.80, 0.95)	0.001
Total duration of antibiotic treatment, days	10.0 (8.0-13.0)	11.0 (8.0-14.0)	0.54 (0.11, 0.98)	0.01	0.35 (-0.12, 0.82)	0.15
Intravenous antibiotic treatment, days	5.0 (3.0-7.0)	6.0 (5.0-9.0)	0.97 (0.55, 1.40)	<0.001	0.78 (0.31, 1.24)	0.001
ICU admission	17 (7.1%)	17 (14.3%)	1.45 (1.14, 1.85)	0.003	1.39 (1.06, 1.81)	0.02
TTCS ^d , days	4.0 (2.0-7.4)	6.0 (3.0-10.0)	0.87 (0.80, 0.94)^a	<0.001	0.87 (0.80, 0.95)^a	0.002
CAP complications ^e	73 (30.4%)	53 (44.5%)	1.23 (1.05, 1.45)^b	0.01	1.14 (0.96, 1.36) ^b	0.15

Data are median (IQR) or *n* (%) unless otherwise stated and adjusted for age, gender, diabetes mellitus, congestive heart failure and renal insufficiency; FGF21 values were log transformed. ^a Hazard ratio, ^b Odds ratio, ^c Regression coefficient. ICU=intensive care unit.

^d TTCS Time to clinical stability defined as defined as time to clinical stabilization of vital signs at two consecutive measurements ≥ 12 h apart.

^e CAP complications defined as recurrence; acute respiratory distress syndrome; empyema; nosocomial infections until day 30; serious adverse events possibly related to CAP; ICU stay; re-admission to hospital.

15. Table S6. FGF21 clinical outcomes in ProCAP trial

			Regression Analysis of Baseline FGF21			
	<u>Tertiles 1-2</u> n=100	<u>Tertile 3</u> n=50	Univariate regression analysis, OR, HR, coefficient (95% CI)	<i>p</i> value	Multivariable adjusted regression analysis, OR, HR, coefficient (95% CI)	<i>p</i> value
Death (30-days)	5 (5.0%)	12 (24.0%)	2.31 (1.45, 3.69)	<0.001	2.13 (1.30, 3.48)	0.002
Time to effective hospital discharge, days	11.0 (9.0-15.0)	13.0 (10.0-14.0)	0.91 (0.79, 1.03)	0.13	0.90 (0.79, 1.03)	0.13
Total duration of antibiotic treatment, days	9.0 (5.0-13.0)	10.0 (4.0-14.0)	0.84 (-0.39, 1.72)	0.06	1.00 (0.01, 1.99)	0.05
Intravenous antibiotic treatment, days	4.5 (3.0-6.0)	4.5 (3.0-6.5)	0.12 (-0.64, 0.60)	0.96	0.18 (-0.61, 0.98)	0.64
ICU admission	13 (13.0%)	7 (14.0%)	1.30 (0.89, 1.88)	0.18	1.49 (0.97, 2.28)	0.07

Data are median (IQR) or *n* (%) unless otherwise stated and adjusted for age, gender, diabetes mellitus, congestive heart failure and renal insufficiency; FGF21 values were log transformed. ^a Hazard ratio, ^b Odds ratio, ^c Regression coefficient. ICU=intensive care unit.

16. References

- 1 Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, Coley CM, Marrie TJ, Kapoor WN. A prediction rule to identify low-risk patients with community-acquired pneumonia. *The New England journal of medicine* 1997; 336: 243–250.