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Original article

Analysis of the effect of pneumonia on mortality (ORACLE-RF)

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Abstract: *Objective* — To analyze the effect of pneumonia on mortality among patients with circulatory decompensation.
Material and methods — The study was based on the *ORACLE-RF* registry containing information obtained from 20 cities in Russia. Patients were monitored for one year. The research included men and women with symptoms of chronic heart failure during circulatory decompensation period. The patients' average age was 67±13 years. Final analysis included 2404 patients.
Results — Hospital mortality was at 9%. By the 30th day of observation, overall mortality rate stood at 13%. Within the year, the overall mortality rate was 43%. Pneumonia and chronic kidney disease (CKD) had the most pronounced effect on death risk – 49.5% and 47.2%. The study showed that patients who do not have pneumonia and CKD among other associated diseases were 2.5 times more likely to survive after 360 days of observation than patients who have them among other associated diseases. The chances of favorable prognosis in patients without pneumonia are 1.7 times higher than in patients with pneumonia among other diseases.
Conclusion — Pneumonia probably triggered the decompensation mechanism and significantly increased mortality in these patients.

Keywords: circulatory decompensation, pneumonia, chronic kidney disease, chronic heart failure.

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Introduction

Analysis of major registries from around the world over the past decade [1–8] has convincingly shown that in-hospital mortality, annual mortality, and rehospitalization after discharge remain extremely high in patients with circulatory decompensation. In most countries, hospitalization for chronic heart failure (CHF) dominates in hospitals. Hospitalization itself is an independent factor in the increasing risk of death in heart failure [9]. In 2013, a survey carried out in 136 centers in 12 European countries among 5,118 patients showed that the mortality rate in patients with circulatory decompensation at 1 year was 17.4%, which is 2.4 times higher than the same indicator in patients who did not have episodes of decompensation within the year [10]. Infectious pulmonary diseases remain one of the leading non-cardiac causes of death in patients with heart failure [11].

Objective: To analyze the effect of pneumonia on mortality among patients with circulatory decompensation.

Material and Methods

Research design

The study was based on the *ORACLE-RF* registry containing information from 20 cities in Russia. Patients were monitored for one year.

The registry included men and women over 18 years old:

i) With symptoms of chronic congestive heart failure of any etiology during the circulation decompensation period requiring hospitalization;

ii) With clinical signs of volume overload, as evidenced by at least two of the following: 1. Shortness of breath or orthopedic position; 2. Bubbling rale; 3. Peripheral edema; 4. Increased jugular venous pulse; 5. Chest x-ray showing signs of stagnation in pulmonary circulation; 6. Plasma BNP level of >150 pg\ml or NT-proBNP level of ≥450 pg\ml.

iii) Those who wish to participate in the registry and sign an informed consent.

Exclusion criteria: This study has no exclusion criteria.

Patients

The study included 2,498 patients. Final analysis included 2,404 patients. Contact with 94 patients (3.76% of the total number of patients) in the post-hospital period was lost (*Appendix* 1, *Appendix* 2).

The clinical profile of the patients is presented in *Table* 1.

Table 1. Clinical profile of patients (n=2,498)

Patient characteristics	*Value*
Age, years	67±13
Female patients, %	53
BMI, kg/m^2	29.5±6.8
BMI>30 kg/m^2, %	33
SBP, mmHg	140±27
DBP, mmHg	84±14
Heart rate, bpm	87±21
Respiration rate, breaths per minute	21±5
Body temperature, ^{0}C	36.6±0.33
Bubbling rale, %	76
Ascites, %	16
Leg swelling, %	73
Ejection fraction, %	48±13
Laboratory findings	
Hemoglobin, g/L	132±22
Leukocytes, 10^9 /l	7.8±3.15
Glycose, mmol/L	5.3 (4.6, 6.6)
Creatinine, mcmol/L	97.0 (80.0, 120.0)
MDRD GFR, ml/min	78.5 (59.0, 100.0)
Urea, mmol/L	7.0 (5.4, 9.6)
Δ creatinine > 0.3 mg/dL (%)	9
CRP, mg/L (on admission)	6.0 (4.0, 16.0)
Total cholesterol, mmol/L	4.8±1.4
Total bilirubin, mmol/L	14.7 (11.0, 21.0)
International Classification of Diseases (ICD)	
Atrial fibrillation, %	48
CHF class III – IV NYHA FC, %	80
CHD, %	77
COPD, %	16
CKD, %	23
Rheumatic heart disease, %	1
Diabetes, %	24
History of acute cerebrovascular accident, %	11
Pneumonia on admission, %	17
Pyelonephritis, %	21
Hepatic cirrhosis, %	8
Trophic ulcers, %	6
Cancer, %	5

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MDRD GFR, estimated glomerular filtration rate using Modification of Diet in Renal Disease (MDRD) formula; CRP, C-reactive protein; CHF, chronic heart failure; CHD, coronary heart disease; COPD, Chronic obstructive pulmonary disease; CKD, chronic kidney disease.

Table 2. Multivariate Cox analysis: Effect of various predictors on mortality

ICD	*Beta*	*p*	*RR*	*95% CI*
Pneumonia	0.204	<0.05	1.22	1.04-1.44
CKD	0.180	>0.05	1.19	1.01-1.41
Cirrhosis	0.130	>0.05	1.15	0.92-1.43
High blood pressure	0.012	>0.05	1.01	0.84-1.21
Atrial fibrillation	0.221	<0.05	1.24	1.09-1.42
COPD	-0.120	>0.05	0.87	0.73-1.04
ACA	0.202	>0.05	1.22	0.99-1.50

χ2= 24.3, p<0.001. CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ACA, acute cerebrovascular accident; RR, risk relation; CI, confidence interval.

Statistical analysis

Analytics software package *Statistica 10* was used to statistically process obtained data. The Shapiro-Wilk test was used to determine that the data set comes from a normal distribution. Methods of nonparametric and parametric statistics were used to present results. Quantitative indicators were presented in the form of mean value with standard deviation – M±SD or median with lower and upper quartiles – Me (LQ, UQ). Multivariate analysis was performed using the Cox proportional hazards model. Survival analysis was evaluated using the Kaplan-Meier method. Logistic regression was used to predict the likelihood of a fatal outcome. The odds ratio (OR) or risk relation (RR) criterion was used to determine the significance of the influence of a particular factor on mortality. Values p<0.05 were recognized as statistically significant.

Results

Overall mortality in patients with circulatory decompensation

The data presented suggests that hospital mortality was 9%. The highest mortality rate was observed in the first 30 days after discharge from hospital. The overall mortality rate by the 30th day of observation was 13%. Moreover, women over 60 years of age had considerably higher mortality – more than that in men of the same age category – 19.4% vs 16%, respectively (p>0.05). During the year, the overall mortality rate was 43%. Analysis of the parameters reflecting patients' comorbid status revealed the ones with the most significant effect on mortality (see *Table* 2). The most pronounced influence on the risk of death came from pneumonia (49.5% mortality), chronic kidney disease (CKD) (47.2% mortality) and cirrhosis (45.7% mortality). This indicates that these conditions are highly significant in the structure of mortality in patients with decompensated chronic heart failure.

Odds ratio of a favorable outcome for patients who have been diagnosed with pneumonia among other associated diseases

For statistical analysis, all patients were divided into groups depending on combination of specific diseases. The following groups were identified:

1. Group 1 – pneumonia + associated diseases (with cirrhosis and/or CKD)

2. Group 2 – pneumonia + associated diseases (without cirrhosis and/or CKD)

The chances of survival in the patients divided into groups with different combinations of associated diseases are as follows: OR1=0.78 and OR2=1.33.

Patients who do not have pneumonia and CKD among other associated diseases are 2.5 times more likely to survive after 360 days of observation than patients who have the two conditions among other associated diseases. The chances of favorable prognosis in patients without pneumonia are 1.7 times higher than in patients with pneumonia among other diseases.

Discussion

Pronounced comorbidity is the most important feature of the modern clinical portrait of a patient with circulatory decompensation. Apart from the widely discussed hypertension and diabetes, it includes coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), CKD, anemia, bacterial chronic and acute diseases.

Our study showed a rather high incidence (17% of cases) of pneumonia than in the often-cited registries [1-10]. For instance,

the Cardiovascular Health Study, analyzing 5880 patients older than 65 years, who were observed for more than 10 years, showed that pneumonia developed in 10% of patients with cardiovascular disease. It was also shown that a combination of heart failure and pneumonia requiring hospitalization increased the risk of death by 4.9 times [12, 13]. In a study by Kaplan et al. [14], the authors analyzed 67,162 patients hospitalized for decompensated heart failure and patients who made up the comparison group without signs of heart failure. Comparison of groups showed that CHF presence increases the risk of developing pneumonia by 1.82 times. The highest risk was observed among patients receiving loop diuretics. In the NHANES I Epidemiologic Follow up study, observation of 5,474 patients over 55 years of age over the course of 12 years showed that pneumonia developed most often among patients with circulatory failure (16%), cancer, diabetes and muscle deficiency. Thus, pneumonia occurs quite often both in patients with decompensated heart failure and in patients with stable course of heart failure, including in the Russian population. Our study (within the ORACLE-RF registry) showed that the risk of death in patients with pneumonia increased significantly more (RR=1.22 [95% CI 1.04; 1.44]) than in the OPTIMIZE-HF registry, where the presence of pneumonia increased the risk of death by only 10.6% [5], or in the V.F. Corrales-Medina meta-analysis (4,215 patients), where increased risk of death was 23.9% [95% CI 16.9-32.6] [15]. Such a result can only be explained by the greater initial comorbidity and the greater initial severity of Russian patients.

Conclusion

So, too many pneumonia cases at the time a patient with decompensated heart failure is hospitalized represents an important feature of the Russian population. Spectrum of bacterial flora in these patients does not always correspond to the classical spectrum of community-acquired pneumonia – a significant proportion in the spectrum of flora is occupied by the flora, which is more typical for hospital-acquired pneumonia. Pneumonia probably triggered the decompensation mechanism and significantly increased mortality in these patients.

Ethical approval

The study was approved by the Ethics Committee of Pirogov Russian National Research Medical University via Report No. 122, dated September 2, 2010.

Limitations

The study did not monitor research centers. The authenticity of the primary information was confirmed by a medical doctor – a researcher. The study was performed in therapeutic and cardiology departments and did not involve resuscitation departments.

Conflict of interest

The authors declare no conflict of interest.

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References

1. O'Connor CM, Stough WG, Gallup DS, Hasselblad V, Gheorghiade M. Demographics, clinical characteristics, and outcomes of patients hospitalized for decompensated heart failure: observations from the IMPACT-HF registry. *J Card Fail* 2005; 11(3): 200-205. https://doi.org/10.1016/j.cardfail.2004.08.160.
2. Rudiger A, Harjola VP, Müller A, Mattila E, Säila P, Nieminen M, et al. Acute heart failure: clinical presentation, one-year mortality and prognostic factors. *Eur J Heart Fail* 2005; 7(4): 662-670. https://doi.org/10.1016/j.ejheart.2005.01.014.
3. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and Outcomes of Patients Hospitalized for Heart Failure in the United States: Rationale, Design, and Preliminary Observations From the First 100,000 Cases in the Acute Decompensated Heart Failure National Registry (ADHERE). *Am Heart J* 2005; 149(2): 209-216. https://doi.org/10.1016/j.ahj.2004.08.005.
4. Zannad F, Mebazaa A, Juillière Y, Cohen-Solal A, Guize L, Alla F, et al. Clinical profile, contemporary management and one-year mortality in patients with severe acute heart failure syndromes: the EFICA study. *Eur J Heart Fail* 2006; 8(7): 697-705. https://doi.org/10.1016/j.ejheart.2006.01.001.
5. Abraham WT, Fonarow GC, Albert NM, Stough WG, Gheorghiade M, Greenberg BH, et al. Predictors of in-hospital mortality in patients hospitalized for heart failure: Insights from the Organized Program to initiate lifesaving treatment in hospitalized patients with heart failure (OPTIMIZE-HF). *J Am Coll Cardiol* 2008; 52(5): 347-356. https://doi.org/10.1016/j.jacc.2008.04.028.
6. Nieminen MS, Brutsaert D, Dickstein K, Drexler H, Follath F, Harjola VP, et al. EuroHeart Failure Survey II (EHFS II): A Survey on Hospitalized Acute Heart Failure Patients: Description of Population. *Eur Heart J* 2006; 27(22): 2725-2736. https://doi.org/10.1093/eurheartj/ehl193.
7. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, et al. Nationwide survey on acute heart failure in cardiology ward services in Italy. *Eur Heart J* 2006; 27(10): 1207 -1215. https://doi.org/10.1093/eurheartj/ehi845.
8. Logear D, Isnard R, Bauer F, Delahaye F, Donal E, Eicher JC, et al. Management of acute heart failure in 2009: the OFICA study. *Arch Cardiovasc Dis* 2011; 3(1): 26. https://doi.org/10.1016/S1878-6480(11)70081-7.
9. O'Connor CM, Miller AB, Blair JE, Konstam MA, Wedge P, Bahit MC, et al. Causes of death and rehospitalization in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction: results from Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) program. *Am Heart J* 2010; 159(5): 841-849 https://doi.org/10.1016/j.ahj.2010.02.023.
10. Maggioni AP, Dahlström U, Filippatos G, Chioncel O, Crespo Leiro M, Drozdz J, et al. EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). *Eur J Heart Fail* 2013; 15(7): 808-817. https://doi.org/10.1093/eurjhf/hft050.
11. Lee DS, Gona P, Albano I, Larson MG, Benjamin EJ, Levy D, et al. A systematic assessment of causes of death after heart failure onset in the community: impact of age at death, time period, and left ventricular systolic dysfunction. *Circ Heart Fail* 2011; 4(1): 36-43. https://doi.org/10.1161/circheartfailure.110.957480.
12. Kaplan V, Angus DC, Griffin MF, Clermont G, Scott Watson R, Linde-Zwirble WT, et al. Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. *Am J Respir Crit Care Med* 2002; 165(6): 766-772. https://doi.org/10.1164/ajrccm.165.6.2103038.
13. O'Meara ES, White M, Siscovick DS, Lyles MF, Kuller LH. Hospitalization for pneumonia in the Cardiovascular Health Study: incidence, mortality, and influence on longer-term survival. *J Am Geriatr Soc*

2005; 53(7): 1108-1116. https://doi.org/10.1111/j.1532-5415.2005.53352.x

14. Kaplan V, Clermont G, Griffin MF, Kasal J, Watson RS, Linde-Zwirble WT, et al. Pneumonia: still the old man's friend? *Arch Intern Med* 2003; 163(3): 317-323. https://doi.org/10.1001/archinte.163.3.317.
15. Corrales-Medina VF, Suh KN, Rose G, Chirinos JA, Doucette S, Cameron DW, et al. Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. *PLoS Med* 2011; 8 6): e1001048. https://doi.org/10.1371/journal.pmed.1001048.

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Appendix 1. Distribution of patients of different age groups by gender, considering the number of rehospitalizations and localization of foci of pneumonia

		Localization	*Number of rehospitalizations*			
			1	2	3	4
50 to 59 years old	Male patients	Right lower lobe	4	0	0	1
		Left lower lobe	0	1	0	0
		Right lower lobe + Left lower lobe	0	2	0	0
		Right lower lobe + Left upper lobe	0	0	1	0
	Female patients	Right lower lobe	4	0	0	0
		Right lower lobe + Left lower lobe	1	0	0	0
60 to 69 years old	Male patients	Right middle lobe	0	0	1	0
		Right lower lobe	6	1	0	0
		Left lower lobe	0	3	2	0
		Right lower lobe + Left lower lobe	4	2	2	0
	Female patients	Right middle lobe	0	0	1	0
		Right lower lobe	11	4	0	0
		Left lower lobe	0	0	0	1
		Right middle lobe + Left lower lobe	0	0	0	0
		Right lower lobe + Left lower lobe	3	1	2	0
70 years and above	Male patients	Right lower lobe	12	3	1	0
		Left lower lobe	1	1	0	0
		Right lower lobe + Left lower lobe	5	0	0	0
		Right middle lobe + Left upper lobe	0	0	1	0
	Female patients	Right middle lobe	5	6	1	0
		Right lower lobe	24	0	1	0
		Left lower lobe	7	0	1	0
		Right lower lobe + Left lower lobe	14	9	0	0
		Right lower lobe + Left upper lobe	0	0	0	2

Appendix 2. Distribution of patients of different age groups by gender, considering frequency of deaths and localization of foci of pneumonia

		Localization	Distribution of deceased/survivors by period								Surv.
			30 days		90 days		180 days		360 days		
			decd.	surv.	decd.	surv.	decd.	surv.	decd.	surv.	
50 to 59 years old	Male patients	Right lower lobe	0	9	2	7	0	7	1	6	9
		Left upper lobe	0	1	0	1	0	1	1	0	1
		Left lower lobe	0	3	0	3	0	3	0	3	3
		Right lower lobe + Left lower lobe	1	3	1	2	0	2	1	1	4
		Surv.	1	16	3	13	0	13	3	10	17
	Female patients	Right lower lobe	1	4	1	3	0	3	0	3	5
		Left lower lobe	0	1	0	1	0	1	0	1	1
		Right lower lobe + Left upper lobe	1	0	0	0	0	0	0	0	1
		Surv.	2	5	1	4	0	4	0	4	7
60 to 69 years old	Male patients	Right middle lobe	0	1	0	1	0	1	0	1	1
		Right lower lobe	1	9	0	9	2	7	1	6	10
		Left lower lobe	0	6	0	6	1	5	1	4	6
		Right lower lobe + Left lower lobe	0	9	1	8	3	5	1	4	9
		Surv.	1	25	1	24	6	18	3	15	26
	Female patients	Right lower lobe	8	11	1	10	1	9	2	7	19
		Left lower lobe	0	1	0	1	0	1	0	1	1
		Right middle lobe + Left lower lobe	1	0	0	0	0	0	0	0	1
		Right lower lobe + Left lower lobe	1	8	1	7	2	5	0	5	9
		Surv.	10	20	2	18	3	15	2	13	30
70 years and above	Male patients	Right lower lobe	6	22	2	20	6	14	1	13	28
		Left lower lobe	1	2	0	2	0	2	0	2	3
		Right lower lobe + Left lower lobe	0	16	2	14	4	10	5	5	16
		Right lower lobe + Left upper lobe	0	1	0	1	0	1	0	1	1
		Surv.	7	41	4	37	10	27	6	21	48
	Female patients	Right middle lobe	5	2	0	2	0	2	0	2	7
		Right lower lobe	15	44	5	39	2	37	5	32	59
		Left upper lobe	0	1	0	1	0	1	0	1	1
		Left lower lobe	4	7	0	7	0	7	1	6	11
		Right lower lobe + Left lower lobe	8	31	7	24	2	22	7	15	39
		Right lower lobe + Left upper lobe	0	2	0	2	0	2	0	2	2
		Surv.	32	87	12	75	4	71	13	58	119

decd., deceased; surv., survivors.