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Research article

ON ASSESSMENT OF THE PROBABILITY OF VARIOUS COMORBIDITIES IN WORKERS OF ALUMINUM AND REFRACTORY INDUSTRIES

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Recent findings in occupational medicine have demonstrated that physical diseases are one of the main factors determining poor health of industrial workers. Non-occupational disorders also have a significant impact on timing of occupational disease onset.

Our objectives were to assess the likelihood of comorbidities in cases of occupational diseases of various etiologies and to compare their profiles.

The study was conducted retrospectively. We created a database of medical records of aluminum and refractory workers and analyzed all diagnoses and systemic disorders identified during the clinical examination of these patients using SPSS Statistics 23. The comorbidity index was used to determine the degree of the disease burden of the subjects. We assessed transnosological and transsystemic multimorbidity, as well as the relationship between multimorbidity and occupational diseases. The Kolmogorov – Smirnov test was used to test the null hypothesis that the set of data came from a normal distribution, after which parametric estimation, Student's t-test, and one-way analysis of variance were applied for data analysis. We established comorbidities that were significantly more frequent among the patients suffering from fluorosis or silicosis.

Exposure to occupational hazards in different industries affects the profile of comorbidity. We observed a pronounced polysystemic nature of lesions in aluminum industry workers and the predominance of comorbid diseases of the respiratory system in refractory workers. The level of multimorbidity among the workers of the refractory industry was significantly lower than that in the aluminum production, thus showing a more pronounced negative impact of the combined occupational risk factors in the latter on workers' health.

Keywords: *occupational disease, comorbidity index, fluorine toxicity, silicosis, combination of occupational hazards, transnosological multimorbidity, transsystemic multimorbidity, aluminum industry, refractory industry.*

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Over the second half of the 20th century, significant progress was made in reducing mortality from acute diseases, shifting the focus on chronic diseases. As the number of deaths from acute diseases decreased, the prevalence of chronic conditions accumulating over time rose. This trend was particularly noticeable in the world where a deteriorating environment made people more vulnerable in the long term (World Health Organization on behalf of the European Observatory on Health Systems and Policies, 2011).

In the 21st century, healthcare systems around the world face the rising burden of chronic diseases posing one of their greatest challenges. According to the World Health Report (2002), longer life expectancy, "modernization" of the lifestyle accompanied by an increasing number of risk factors for many chronic diseases, and growing opportunities of saving lives of people who were previously terminally ill, lead to a change in the structure of morbidity, which in turn affects healthcare in different countries.

The World Health Organization (WHO) recognizes that chronic conditions "require ongoing management over a period of years or decades". This category includes a variety of diseases and disorders that fall outside the standard definition of a "chronic disease," i.e. coronary heart disease (CHD), diabetes mellitus, or bronchial asthma [1].

In the context of the pandemic of chronic diseases, the relationship between them is widely discussed being one of the key areas of research in various fields of medicine. "In patient with a particular index disease, the term co-morbidity refers to any additional co-existing ailment", either with pathogenetic interplay or common chronometric features[1].

Comorbidity types include the following [2–4]:

1. Causal comorbidity, which occurs when different organs and systems are affected by the same pathological mechanism;

2. Complicated comorbidity, which is the outcome of the index disease and its consequences;

3. Iatrogenic comorbidity, which manifests itself following complications of medical treatment or examination, provided that their danger is known in advance;

4. Unspecified comorbidity, which suggests the presence of common mechanisms for the development of diseases in this combination, but requires additional research to confirm the hypothesis; and

5. "Random" comorbidity representing a random combination of diseases lacking logical reasoning.

Many authors stick to this classification [5–8].

There exist several scales for assessing comorbid disorders, such as the Cumulative Illness Rating Scale (CIRS), the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), Kaplan–Feinstein index (KFI), the Index of Coexistent Diseases (ICED), the Geriatric Index of Comorbidity (GIC), Charlson comorbidity index (CCI), the Total Illness Burden Index (TIBI), the Chronic Disease Score (CDS), the Adjusted Clinical Groups (ACG) system, the Functional Comorbidity Index (FCI), etc.[2] [3, 9–17]. These scales help analyze the condition

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of patients, including the elderly ones, and predict mortality. Comorbidity indices play an important role in managing the impact of comorbid diseases on patients in the long term. Each of these indices has its own advantages and disadvantages and is used in different clinical situations.

We have come across only few articles discussing combinations of occupational and general diseases in workers exposed to occupational dangers and hazards [18–20].

Here we consider the relationship between general physical disorders, occupational risk factors, and the development of occupational diseases in workers of aluminum and refractory industries.

Inorganic fluorine compounds, high concentrations of which are detected in the workplace air, are among the main hazards in aluminum production. Working conditions of the core personnel (electrolysis operators and anode makers) correspond to Classes 3.3 and 3.4 [21]. Chronic fluorine poisoning, or occupational fluorosis, ranks highest in the structure of occupational diseases in the industry.

With various routes of exposure to inorganic fluorine compounds, their toxic effects are attributed to the resorption of fluorine ions. Fluorine chemicals can induce a variety of metabolic disorders, including those of lipid and carbohydrate metabolism, by suppressing the activity of enzyme systems inside cells. Acting as a multienzyme poison, the fluorine ion is believed to suppress the activity of more than 60 enzymes. In the clinical picture of occupational diseases, there is such a condition as fluorosis – a chronic poisoning that develops following long-term and high-dose exposure to fluorine and its compounds. A characteristic and specific sign of fluorosis is damage to the musculoskeletal system described as fluorine osteopathy [22]. At the same time, other organs and systems, including hepatobiliary, cardiovascular, autonomic, nervous, endocrine, and digestive ones, may be involved in the pathological process. In most cases, the disease develops after ten years of occupational exposure (depending on the airborne levels of fluorine compounds and their ability to dissolve). Currently, the mean latent period of occupational fluorosis is 20 years[3]. Given the present-day concentrations of fluorine compounds in the workplace air, the disease may develop much earlier in highly sensitive workers.

The core personnel involved in the production of aluminum by electrolysis are molten salt electrolysis operators, anode makers, and bridge crane operators. Service personnel, such as electricians and equipment repair workers, spend up to 76.3 % of their shift time near shop-floor equipment and are exposed to the same occupational hazards as the core workers, but receive different doses.

S.V. Shcherbakov was the first to predict the likelihood of developing occupational chronic fluorine poisoning depending on the cumulative dose of fluorine since the first contact[4]. Multivariate analysis techniques were used to substantiate indicators for diagnosing the initial stage of occupational fluorosis out of many symptoms describing the state of the musculoskeletal system and metabolism. The analysis, however, did not reveal specific clinical signs of its early stage, thus necessitating consideration of both radiological and clinical parameters ensuring an individual approach to particular cases.

Respiratory diseases are one of the key issues in contemporary occupational medicine [23]. Lung injuries caused by exposure to industrial aerosols rank second in the structure of occupational diseases. According to the current classification, pneumoconioses are a group of interstitial lung diseases with known etiology.

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[3] Zhovtyak E.P., Odinokaya V.A., Semennikova T.K., Yarina A.L. [et al.]. Khronicheskaya professional'naya intoksikatsiya ftorom i ego soedineniyami – flyuoroz: posobie dlya vrachei [Chronic Occupational Poisoning with Fluorine and Its Compounds – Fluorosis: A Manual for Physicians]. Yekaterinburg, 2003, 16 p. (in Russian).

[4] Shcherbakov S.V. Gigiena truda v proizvodstve i primenenii neorganicheskikh ftoridov [Occupational health in the production and use of inorganic fluorides]: Doctoral thesis. Sverdlovsk, 1989, 378 p. (in Russian).

Refractory workers are exposed to a combination of risk factors, the main of which are highly fibrogenic aerosols. Dust is generated at each stage of the production of refractory materials.

Press, mill, and conveyor operators, mechanics and other workers serving grinding and molding machines are exposed to the highest levels of dust at work [24]. Dinas refractories are the most common type of refractory products. Dinas production involves the extensive use of silica and induces occupational lung diseases in the modern production of silicate products. Other risk factors of refractory manufacturing include irritant gases, resinous substances, hot microclimate, and heavy physical work [25]. The combination of the above risk factors poses a higher risk of occupational diseases of the bronchi and lungs.

The **objectives** of our study were to assess the likelihood of developing comorbidities in patients with different occupational diseases and to compare their profiles.

Materials and methods. We applied a retrospective approach including the analysis of all diagnosed diseases regardless of their status (index or concomitant) in each patient. The disease burden was determined using the multimorbidity index, where the number of diseases was divided by the number of patients [26]. We also assessed multimorbidity by nosology (the number of different physical diseases) and by system (the number of affected systems in each patient) [6].

The Kolmogorov – Smirnov test was used to test the null hypothesis that the set of data came from a normal distribution, after which parametric estimation, Student's *t*-test, and one-way analysis of variance were applied. The results are presented as $M \pm m$ where m is the error of the arithmetic mean M. The level of significance was set at 0.05 ($\alpha = 0.05$ or $p < 0.05$).

Results and discussion. We did a multivariate analysis of medical records of 192 male workers aged 32 to 75 years (mean: 53.48 ± 0.57 years) with the mean occupational exposure of 22.58 ± 0.42 years (range: 7 to 35 years) employed in the aluminum industry. The case group consisted of 93 patients (48.5 %) with occupational fluorosis (mean age: 57.85 ± 0.65 years; mean occupational exposure duration: 22.74 ± 0.65 years). The reference group included 99 workers without occupational poisoning (mean age: 49.35 ± 0.70 years; mean occupational exposure duration: 22.61 ± 0.56 years). The analysis showed no statistical difference between the groups in terms of exposure duration ($p = 0.874$). Yet, the patients suffering from occupational fluorosis were found to be significantly older ($p < 0.001$; Mann – Whitney U test).

We also analyzed medical histories of 172 workers of Pervouralsk Dinas Plant OJSC examined in the Occupational Health Clinic of the Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers. The main group included 75 patients with a confirmed diagnosis of silicosis; 97 experienced workers without occupational diseases were matched by sex (the proportion of men in the groups was 53 and 68 %, respectively, $p = 0.052$) and duration of dust exposure (21.11 ± 1.03 vs 20.85 ± 1.05 years, respectively, $p = 0.862$) as controls. Workers from the main group were older (55.84 ± 0.96 vs 49.72 ± 0.84 years, respectively, $p < 0.001$).

The study cohorts are described in Table 1.

Table 1

Description of the study cohorts

Parameter	Aluminum production	Refractory production
Workers, *n*	192	172
Mean age, years	53.48 ± 0.57	55.84 ± 0.96
Mean work experience, years	22.58 ± 0.42	21.11 ± 1.03

The number of comorbid diseases (nosological multimorbidity) per patient with

fluorosis was 6.95 ± 0.26, and 5.18 ± 0.22 per experienced worker ($p < 0.001$). The number of affected body systems (systemic multimorbidity) per patient with occupational fluorine poisoning was 5.71 ± 0.20 and 3.98 ± 0.16 per control ($p < 0.001$).

The following comorbid diseases and conditions were significantly more prevalent in the fluorosis cases compared to the controls: obesity (47 % vs 31 %, respectively, $p = 0.018$), type 2 diabetes mellitus (17 % vs 4 %, $p = 0.003$), arterial hypertension (68 % vs 45 %, $p = 0.001$), heart failure (28 % vs 4 %, $p < 0.001$), atrial fibrillation (15 % vs 0 %, $p < 0.001$), atrophic gastritis (65 % vs 24 %, $p < 0.001$), hyperuricemia (41 % and 13 %, $p < 0.001$), fatty liver disease (48 % vs 24 %, $p = 0.003$), serum creatinine level (84.45 ± 1.98 vs 76.85 ± 1.30 μmol/L, $p = 0.002$), and chronic kidney disease (73 % vs 27 %, $p < 0.001$).

Fluorine exposure indicators also differed statistically in terms of the frequency of hydrofluoride levels above the maximum allowable concentration (MAC) (36 % vs 11 %; $p = 0.002$) and above 2 MAC (90 % vs 60 %, $p < 0.001$), which had probably determined the development of occupational fluorine poisoning in the case group.

In the reference group of experienced workers, no cases of atrial fibrillation were registered. Yet, the development of pneumoconiosis was significantly more often observed in them than in the fluorosis cases (7 % vs 0 %, respectively, $p = 0.007$).

X-ray changes corresponding to Stage 1 fluorosis were registered in 39 % of the workers with fluorosis ($p = 0.002$), and those corresponding to Stage 2 fluorosis were registered significantly more often in fluorosis cases (75 % vs 36 %, $p < 0.001$). X-ray images characteristic of Stage 3 fluorosis were obtained only for four workers with occupational fluorine poisoning (4.3 %).

We observed, on the average, 4.27 ± 0.22 comorbid diseases per silicosis case and 2.39 ± 0.17 diseases per experienced worker ($p < 0.001$). As for systemic multimorbidity, patients with pneumoconiosis and experienced workers had, on the average, 3.76 ± 0.19 and 2.21 ± 0.15 affected systems, respectively ($p < 0.001$).

The following functional respiratory disorders were statistically more frequent in the silicosis cases compared with the workers without occupational diseases: decreased vital capacity (VC) of the lungs – 83.42 % vs 93.34 % ($p = 0.003$); reduced forced expiratory volume per second (FEV1) – 2.33 ± 0.08 L/sec vs 3.77 ± 0.83 L/sec ($p = 0.89$); relative FEV1 decline – 77.8 ± 2.36 % vs 89.84 ± 1.9 % ($p < 0.001$); decreased forced vital capacity (FVC) – 3.70 ± 0.11 m^3 vs 2.89 ± 0.12 m^3 ($p < 0.001$), and relative FVC decline – 78.39 ± 2.59 % vs 93.35 ± 2.15 % ($p < 0.001$), respectively.

The rates of the following comorbidities were also statistically higher in the group of workers with occupational diseases: left ventricular hypertrophy (LVH) (48 % vs 20 %, $p = 0.003$), heart failure (25 % vs 2 %, $p < 0.001$), and arrhythmia (15 % vs 1 %, $p = 0.018$).

The 8-hour time weighted average dust concentration was found to be statistically higher in the group of workers with silicosis (3.19 ± 0.26 vs 1.87 ± 0.13 mg/m^3, respectively, $p < 0.001$) and might have caused the development of pneumoconiosis in those workers.

To assess the probability of developing multimorbidity in fluorosis cases and the coefficient of multimorbidity (integrated comorbidity), we built a model using logistic regression and determined the predictors of the regression equation. To exclude correlations between the predictors that could negatively affect the quality of the model (i.e., the identifiability of equation parameters), we used the method of step-by-step variable selection - Forward LR.

The obtained coefficients of the logistic regression equation are presented in Table 2.

Table 2

Coefficients of the logistic regression equation used to predict the development of multimorbidity (multimorbidity coefficient)

Predictors	B	SE	Sig.	exp (B), odds ratio
BMI	0.199	0.084	0.017	1.221
Fluorosis	5.720	1.622	0.000	305.032
HDL	-4.234	1.410	0.003	0.014
CMD	2.665	1.008	0.008	14.363
Constant	-2.053	2.807	0.465	0.128

N o t e s: B – coefficient in the logistic regression equation for the corresponding predictor; SE, standard error of the mean; Sig. – statistical significance of coefficient B; exp (B) – odds ratio per unit change in the predictor (factor); BMI, body mass index; HDL, high-density lipoproteins; CMD, carbohydrate metabolism disorders.

The formula (1) for the logistic regression equation and further calculation of the probability of developing multimorbidity in the workers of interest is as follows:

$$y = -2.053 + 0.199 \cdot \text{BMI} + 5.720x_1 - 4.234 \cdot \text{HDL level} + 2.665x_2, \quad (1)$$

where $x_1 = 1$ for the diagnosis of fluorosis and $x_1 = 0$ for its absence; $x_2 = 1$ for carbohydrate metabolism disorders and $x_2 = 0$ for their absence in the worker.

Then the probability (P) of developing multimorbidity (multimorbidity coefficient) will be calculated as follows:

$$P = \exp(y) / (1 + \exp(y)). \quad (2)$$

The formula for assessing the likelihood of developing multimorbidity covers the following factors: body mass index, high-density lipoprotein levels, diagnosed fluorosis, and the presence of carbohydrate metabolism disorders. According to the classification table, the constructed model has a high overall predictive ability (86.7 %). Moreover, in the case of predicting the outcome of interest, the model has high specificity (90.4 %) and high sensitivity (80.6 %).

Based on the results of assessing comorbidities among workers in hazardous industries, the highest prevalence of comorbid diseases and conditions was registered among the aluminum industry workers. The maximum nosological comorbidity in them equaled 6.95, meaning that almost seven comorbid diseases or conditions were diagnosed in patients with fluorosis, such as: hypertension, type 2 diabetes mellitus, obesity, heart failure, atrial fibrillation, atrophic gastritis, fatty liver disease, abnormal serum creatinine levels, and/or chronic kidney disease.

This implies that, of the nine diseases or conditions listed, five (55.5 %) were cardiovascular disorders, two were gastrointestinal diseases, and the other two were diseases of the excretory system. Systemic multimorbidity in the workers with fluorosis was 5.18 ± 0.22, meaning that more than five systems were affected in each patient: the cardiovascular and excretory systems, liver, kidneys, and metabolism. Such a wide profile of comorbid diseases and affected systems is related to the fact that fluorine is a multienzyme, multisystem poison.

In the reference group, the number of comorbid diseases per experienced worker was 5.18 ± 0.22, i.e. significantly lower than in patients with fluorosis ($p < 0.001$). The number of affected body systems (systemic multimorbidity) per experienced worker was 3.98 ± 0.16, which was also significantly lower than in the fluorosis cases ($p < 0.001$). This pattern is probably due to the fact that fluorine exposure of workers with fluorosis was statistically higher. The absence of chronic kidney disease and atrial fibrillation

in the reference group was potentially related to its lower exposures since the pathogenetic basis of these disorders includes fibrosis and inflammation.

In the silicosis cases, we established, on the average, 4.27 ± 0.22 comorbid diseases per patient, while in the reference group this number was 2.50 ± 0.27 ($p < 0.001$). As for systemic multimorbidity, 3.53 ± 0.22 systems on the average were affected in the pneumoconiosis patients compared to 2.20 ± 0.22 in the controls ($p < 0.001$). That is, more than four of the following comorbidities were registered per silicosis case: hypertension, silicosis, respiratory failure, coronary heart disease, obesity, lipid metabolism disorders, etc.

When comparing comorbid disorders in refractory workers without occupational diseases, we noticed the absence of left ventricular hypertrophy (LVH), underweight, type 2 diabetes mellitus, elevated levels of interleukins 4 and 8 in them. On the other hand, in the group of workers with silicosis, there were no cases of urolithiasis, increased intima-media thickness, or kidney cysts. In the workers with occupational silicosis, compared with experienced refractory workers, decreased vital capacity of the lungs (82.7 ± 2.9 % vs 93.1 ± 3.9 %, $p = 0.034$), FEV1 (54 % vs 29 %, $p = 0.017$), and FVC (76.1 ± 3.4 % vs 90.5 ± 3.9 %, $p = 0.07$) were statistically more frequent.

The number of affected body systems (systemic multimorbidity) per patient with pneumoconiosis was 3.53 ± 0.22 vs 2.20 ± 0.22 per an experienced worker ($p < 0.001$). We assume that a more frequent development of general diseases and a greater number of affected systems in the group of workers with pneumoconiosis (silicosis) are associated with a higher 8-hour time weighted average dust concentration in the workplace (2.40 ± 0.25 vs 1.72 ± 0.23 mg/m^3, respectively, $p = 0.051$).

It is worth mentioning that the level of both nosological and systemic multimorbidity in refractory workers is significantly lower than that in the workers of aluminum industry, which allows us to conclude that the combination of occupational hazards in refractory manufacturing has a less pronounced negative impact on workers' health and mainly induces comorbid diseases of the respiratory and cardiovascular systems, and metabolic disorders. The likelihood of developing pneumoconiosis depends on several factors, occupational dust exposure being of greatest importance, followed by a high cumulative exposure dose of inorganic dust and genetic predisposition to dust-induced pulmonary fibrosis. If the exposure level, chemical composition and dispersion of dust give an idea of working conditions in various industries, then the rates of nosological and systemic comorbidity help establish the extent of health problems and lesions characteristic of various industries.

Here are the examples of using the model to calculate probability.

Patient A: BMI = 26 kg/m^2, HDL = 1 mmol/L, has carbohydrate metabolism disorders but no fluorosis. For patient A, according to formula (1), we have:

$$y = 0.199 \cdot 26 - 4.234 \cdot 1 + \\ + 2.665 - 2.053 = 1.552$$

Using formula (2), the probability of developing multimorbidity in patient A is estimated as follows:

$$P = \exp(y) / (1 + \exp(y)) = 0.825, \text{ or } 82.5\ \%$$

Patient B: BMI = 23 kg/m^2, HDL = 1.2 mmol/L, no carbohydrate metabolism disorders or fluorosis. For patient B, we have:

$$y = 0.199 \cdot 23 - 4.234 \cdot 1.2 - 2.053 = -2.5568$$

The probability of developing multiple long-term conditions in this patient is as follows:

$$P = \exp(y) / (1 + \exp(y)) = 0.0719, \text{ i.e. } 7.19\ \%$$

Conclusions:

1. At present, the structure of morbidity is dominated by chronic, multifactorial diseases,

characterized by multimorbidity and multisystemic lesions.

2. Combinations of occupational risk factors in various industries form different profiles of comorbidities. In the aluminum industry, we observed a pronounced polysystemic nature of lesions, while respiratory diseases prevailed in refractory workers.

3. The fluorosis cases have a significant number of comorbid and systemic diseases: more than six comorbidities with more than four systems affected on the average, which is probably due to the properties of fluorine compounds as a multienzyme and multisystem poisons.

4. Risk factors of refractory manufacturing have a less pronounced negative impact on workers' health (silicosis cases have, on the average, slightly more than four comorbid diseases with 3.5 systems affected).

5. The use of such indicators as nosological and systemic multimorbidity allows not only to assess the individual degree of health impairment, but also to compare characteristics of lesions specific for different industries.

Compliance with ethical standards. The study complied with ethical standards of the World Medical Association Declaration of Helsinki on the Ethical Principles of Scientific Medical Research Involving Human Subjects as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" adopted by Order of the Ministry of Health of the Russian Federation No. 266 of June 19, 2003. It was approved by the Ethics Committee of the Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers (protocol No. 7 of October 3, 2022).

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