Disseminated invasive aspergillosis.
Results of retrospective analysis of the large register.

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Materials and methods
Retrospective analysis of patients with disseminated proven and probable IA in 1998-2019 yy. We used criteria EORTC/MSG, 2008 for the diagnosis of proven and probable IA.

Results
In 1998-2019 yy we observed 803 patients with proven (12%) and probable (88%) IA. Disseminated IA was diagnosed in 75 (9%) patients, median age – 35 years (1 – 99), children and adolescents – 23%, males – 50%. The comparison group consisted 728 patients, median age – 42 years (1 – 86), children and adolescents – 15%, males – 56%. In both groups IA predominantly occurs in patients with hematologic malignancies (82% vs 87%). The disseminated IA more often developed in patients with acute leukemia (60% vs 42%, p < 0.05), significantly less often in patients with lymphomas (8% vs 28%, p < 0.05) and multiple myeloma (1% vs 6%, p < 0.05), (Fig.1).

Non-hematologic underlying diseases were 18% and 13%, respectively; there were no disseminated IA in patients with chronic obstructive pulmonary disease and tuberculosis. The main risk factors for the IA development in both groups were persistent severe neutropenia (83% vs 73%) and lymphocytopenia (78% vs 60%, p < 0.05), steroids use (67% vs 65%), long-term immunosuppressive therapy (38% vs 27%, p < 0.05), GVHD after allo-HSCT (29% vs 19%, p < 0.05), and ICU stay (20% vs 14%, p < 0.05), (Fig. 2,3).

The main sites of infection were lungs (92% vs 95%). Sinuses (43% vs 1.5%, p<0.05) and central nervous system involvement (40% vs 1.5%, p < 0.05) more often occurred in disseminated IA group (Fig.4 a,b).

In patients with disseminated IA were more often observed respiratory failure (51% vs 36%, p < 0.05), CNS symptoms (32% vs 1%, p < 0.05). The main causative agents were A. fumigatus (45% vs 51%), A. niger (23% vs 29%), and A. flavus (26% vs 14%). Disseminated IA was more often caused by ≥2 Aspergillus spp. (35% vs 9%, p<0.05).

Antifungal therapy was used in 96% vs 99% patients. The overall 12-week survival rate for disseminated IA was significantly lower (63% vs 82%, p < 0.05).

Conclusions
Disseminated IA developed in extremely immunocompromised patients with acute leukemia (60%), persistent severe lymphocytopenia (78%), long-term immunosuppressive therapy (38%), and GVHD after allo-HSCT (29%). The main pathogens were A. fumigatus (45%), and ≥2 Aspergillus spp. (35%). The main sites of disseminated IA were lungs – 92%, sinuses – 43%, and CNS – 40%. Respiratory failure (51%) and CNS symptoms (32%) were frequent in disseminated IA group. The overall 12-week survival rate of disseminated IA patients was significantly lower than the main cohort (63% vs 82%, p < 0.05).