**Objectives**: To evaluate the diagnostic accuracy of *Aspergillus* droplet digital PCR (ddPCR) in exhaled breath condensate (EBC) and broncholaveolar lavage (BAL) samples for diagnosing invasive pulmonary aspergillosis (IPA) in patients with hematological malignancies undergoing bronchoscopy.

**Materials & Methods:** We prospectively enrolled patients with acute leukemia or those who had undergone allogeneic hematopoietic stem cell transplantation (HSCT) and required bronchoscopy for the evaluation of pulmonary infiltrates. The study was conducted between October 2021 and September 2024. BAL fluid was collected during the bronchoscopy, and an EBC sample was obtained within 48 hours using an Rtube© device. *Aspergillus* DNA was detected using ddPCR, using both pan-*Aspergillus* and *Aspergillus fumigatus*-specific primers. The limit of detection for each sample type was calculated based on serial dilutions of stock *Aspergillus* DNA. BAL samples were routinely sent for fungal smear, fungal culture and galactomannan testing. Serum galactomannan was collected as part of standard care. The primary outcome was the diagnosis of probable or proven IPA, as defined by the EORTC/MSG criteria. We calculated sensitivity, specificity, positive predictive value, negative predictive value, and positive and negative likelihood ratios for EBC and BAL ddPCR using a generalized lineal model.

**Results**: Overall 196 patients undergoing 209 bronchoscopies were enrolled. We obtained 194 BAL fluid samples and 188 viable EBC samples (>0 ml). The median age was 62.5 years (IQR 52-69) and 66.3% (130/196) were male. The most common underlying hematologic malignancy was acute myeloid leukemia (76%, 149/196), followed by acute lymphoid leukemia (10.2%, 20/196) and myelodysplastic syndrome (5.1%, 10/196). The most frequently administered chemotherapy regimens were induction (33.7%, 66/196), salvage (15.3%, 30/196) and conditioning for HSCT (7.1%, 14/196), while 30% (58/196) were not on active chemotherapy at the time of bronchoscopy. Patients post-allogeneic HSCT made up 28.1% (55/196) of the cohort. Overall 27 patients (13.8%) were diagnosed with probable or proven IPA. Microbiologic diagnosis in these patients was based on positive galactomannan in BAL in 21 (80.8%), positive serum galactomannan in 9 (34.6%) and *Aspergillus* growth in culture in 5 (19.2%).

In EBC samples, *Aspergillus* ddPCR had a sensitivity of 8.3% (95% CI 1%-27%) and a specificity of 93.3% (95% CI 88.3%-96.6%) for diagnosing probable/proven IPA. Using a tiered diagnostic approach, the number needed to test to prevent one bronchoscopy was estimated at 15. Similar results were observed when limiting the analysis to patients not receiving anti-mold therapy at the time of testing (79/188) or to those whose EBC volume exceeded 0.5 ml (160/188).

In BAL samples, *Aspergillus* ddPCR demonstrated a sensitivity of 43.5% (95% CI 23.2%-65.5%) and a specificity of 88.3% (95% CI 82.5%-92.7%). These values remained consistent when limiting the population to patients off anti-mold coverage at the time of testing (87/194). Notably, ddPCR in BAL showed improved performance for diagnosing culture-positive IPA, with sensitivity of 80% and specificity of 86.2%.

**Conclusions**: *Aspergillus* ddPCR in EBC and in BAL demonstrated high specificity but low sensitivity for diagnosing IPA, limiting its utility as a diagnostic tool. Further research is needed to understand the factors contributing to this.