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MAJOR ARTICLE

A Systematic Literature Review to Determine Gaps in Diagnosing Suspected Infection in Solid Organ Transplant Recipients

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Background. Improved diagnostic testing (DT) of infections may optimize outcomes for solid organ transplant recipients (SOTR), but a comprehensive analysis is lacking.

Methods. We conducted a systematic literature review across multiple databases, including EMBASE and MEDLINE(R), of studies published between 1 January 2012–11 June 2022, to examine the evidence behind DT in SOTR. Eligibility criteria included the use of conventional diagnostic methods (culture, biomarkers, directed-polymerase chain reaction [PCR]) or advanced molecular diagnostics (broad-range PCR, metagenomics) to diagnose infections in hospitalized SOTR. Bias was assessed using tools such as the Cochrane Handbook and PRISMA 2020.

Results. Of 2362 studies, 72 were eligible and evaluated heterogeneous SOT populations, infections, biospecimens, DT, and outcomes. All studies exhibited bias, mainly in reporting quality. Median study sample size was 102 (range, 11–1307). Culture was the most common DT studied (N = 45 studies, 62.5%), with positive results in a median of 27.7% (range, 0%–88.3%). Biomarkers, PCR, and metagenomics were evaluated in 7, 19, and 3 studies, respectively; only 6 reported sensitivity, specificity, and positive/negative predictive values. Directed-PCR performed well for targeted pathogens, but only 1 study evaluated broad-range PCR. Metagenomics approaches detected numerous organisms but required clinical adjudication, with too few studies (N = 3) to draw conclusions. Turnaround time was shorter for PCR/metagenomics than conventional diagnostic methods (N = 4 studies, 5.6%). Only 6 studies reported the impact of DT on outcomes like antimicrobial use and length of stay.

Conclusions. We identified considerable evidence gaps in infection-related DT among SOT, particularly molecular DT, highlighting the need for further research.

Keywords. diagnostic testing; infection; solid organ transplant.

Infection is a major cause of morbidity and mortality in solid organ transplant recipients (SOTR) [1, 2]. However, challenges in determining the underlying etiology contribute to increased empiric antimicrobial use, multidrug-resistant organism acquisition, prolonged hospitalization, allograft failure, and mortality [3–5]. Diagnosing infections in SOTR is challenging because of the broad spectrum of potential infections, atypical presentations, and overlap with other conditions. Rejection, posttransplant lymphoproliferative disease, and serum sickness from antithymocyte globulin may present as nonspecific febrile syndromes, often necessitating extensive workups and unwarranted antimicrobials [6]. Radiographic findings cannot reliably distinguish infectious from noninfectious lesions. For example, central nervous system (CNS) imaging in JC virus infection and posttransplant lymphoproliferative disease can appear identical [7], and chest computed tomography scans cannot identify whether lung nodules are caused by fungi, *Nocardia*, *Mycobacteria*, or malignancies [8]. Donor-derived infections (DDI) represent a diagnostic challenge that is unique to SOTR; DDI often present atypically or are diagnosed late, resulting in poor outcomes [9–13]. Invasive procedures (eg, biopsies, lumbar punctures, bronchoscopies) are often pursued in an attempt to determine the diagnosis but can carry substantial risks [14, 15]. As a result, transplant clinicians commonly perform multiple tests simultaneously or sequentially [2] to optimize diagnostic yield.

Diagnostic testing (DT) for infections in SOTR, as in other populations, can be categorized as culture-based or non–culture-based. Cultures are inexpensive and enable susceptibility

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testing but may have poor sensitivity or slow turnaround times (TAT) depending on the pathogen or specimen [16, 17] and can yield false-negative results if antimicrobials have been prescribed [18–20]. Lifelong immunosuppression in SOTR blunts immune responses, reducing the yield of antibody-based testing [21]. In SOTR, serum fungal diagnostic assays detecting [1,3]-beta-D-glucan (BDG) or the *Aspergillus* galactomannan (GM) are limited by non-specificity or low sensitivity, respectively [16, 17, 22–24], although GM sensitivity improves with bronchoalveolar lavage fluid (BALF) testing following bronchoscopies [25]. *Cryptococcus* [26] and *Histoplasma* [27] antigen tests are accurate but have variable institutional TATs (eg, send-out testing) [28–31] and are also underutilized because of underrecognition of these syndromes [32, 33]. Additionally, antibody/antigen-based tests are "hypothesis-driven" [34] and generally require clinicians to consider and test for specific pathogens in their differential diagnoses.

Although there has been widespread adoption of molecular diagnostic testing (MDT) platforms, including some that use non-invasive specimens like blood, MDT technologies have important limitations. Polymerase chain reaction (PCR) testing, whether targeting a single pathogen or multiple pathogens (eg, multiplex panels for respiratory, CNS, or gastrointestinal syndromes), is now part of conventional DT in SOT [35]. However, these tests are hypothesis-driven and limited to a predefined array of pathogens [36], with performance varying by assay and pathogen [37, 38]. Broad-range PCR (BRPCR), which amplifies conserved regions in bacterial (eg, 16S rRNA) or fungal (eg, 28S rRNA) genomes, is hypothesis-free and can theoretically identify any bacteria or fungi in the sequencing database but cannot detect viruses or parasites and may be less sensitive than conventional PCR depending on the platform, specimen, and pathogen [39]. Recent years have seen a proliferation of novel MDT technologies, such as metagenomic sequencing [39–42]. Unlike other MDT, metagenomic sequencing leverages large sequencing databases to detect prokaryotes, eukaryotes, and viruses through a pathogen-agnostic or "hypothesis-free" approach [42] and from a variety of specimens [41–45].

Despite the pressing need to optimize infection DT in SOTR, a comprehensive review of existing methods lacking. Thus, we conducted this systematic literature review (SLR) to comprehensively characterize the current infection DT landscape in SOTR and identify evidence gaps to guide future research.

MATERIALS AND METHODS

Systematic Literature Review

We used a comprehensive search strategy (Supplementary Methods) across multiple bibliographic databases and other public sources from 1 January 2012 through 11 June 2022 to identify contemporary data on diagnosing infections in SOTR. Eligible studies included those evaluating hospitalized adult or pediatric SOTR with suspected infections using conventional diagnostic methods (CDM; ie, culture, serology, antigen testing, nonmolecular biomarkers, and pathogen-directed or multiplex PCR) or advanced molecular diagnostics (ie, BRPCR, metagenomic testing) regardless of the platform manufacturer (academic, commercial, other). Because our objective was to evaluate the broader infectious disease diagnostic landscape, we excluded studies that only discussed a single pathogen. Details of study selection and data extraction methods are provided in Supplementary Tables 1–7.

Synthesis of Results

Our methodology adhered to established guidelines (Cochrane Handbook for Systematic Reviews of Interventions [46] and the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA] 2020 statement [47]). Bias risk assessment is described in the Supplementary Methods. We evaluated the performance characteristics of DTs, including pathogen yield or detection rates, accuracy metrics (sensitivity, specificity, positive predictive values [PPV]/negative predictive values [NPV]), and turnaround time. We also assessed whether studies reported the following measures: clinical course (including antimicrobial management), clinical outcomes (including morbidity, graft loss, and mortality), healthcare resource utilization (HCRU), and cost. Finally, we examined whether studies evaluated the impact of infection DT on these metrics.

RESULTS

Study Selection

The database searches identified 2362 unique records. After classification using the original Population, Intervention, Comparators, Outcomes, Timing, and Study design (Supplementary Table 3), applying additional exclusion criteria (Supplementary Tables 4–6), and conducting a full-text review, 70 records were deemed eligible (Figure 1, PRISMA flow diagram). We identified 2 additional studies through supplementary searches (Supplementary Table 2). Thus, 72 unique studies were included.

Study Characteristics

Study characteristics are shown in Figure 2 (Supplementary Table 8). Median patient sample size was 102 (range, 11–1307; Q1/Q3, 57.5/200; Figure 2*A*). Studies were stratified by SOT type as follows: lung (pediatric [48, 49], n = 2; adult [45, 50–60], n = 12), liver (pediatric [61–64], n = 4; adult [65–86], n = 22), kidney (pediatric [87], n = 1; adult [88–106], n = 19), heart (pediatric, n = 0; adult [107], n = 1), pancreas (pediatric, n = 0; adult [108], n = 1), and >1 organ (pediatric [109], n = 1; adult [110–118], n = 9; Figure 2*B*). Studies originated from diverse regions (North America, n = 16; Europe, n = 23; and Asia, n = 22; Supplementary Figure S1). Most studies

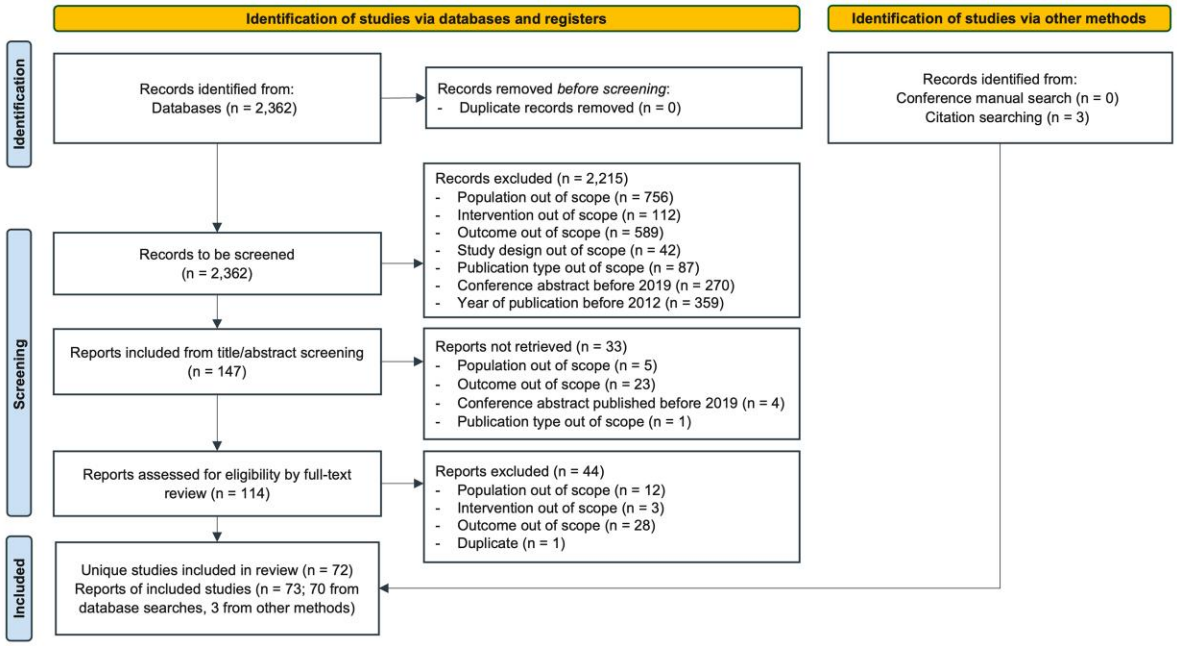

Figure 1. Study selection—PRISMA flow diagram for the systematic literature review, 1 January 2012–11 June 2022. Overall, 72 unique studies were included in the review. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

(n = 45, 62.5%) evaluated standard cultures (Table 1); 11 (15.3%) evaluated blood biomarkers (*Aspergillus* GM, BDG, or C-reactive protein [CRP], n = 5; serology, n = 6). Overall, 21 studies (29.2%) examined MDT: PCR (n = 17, 23.6%), bacterial BRPCR (n = 1), and metagenomics (n = 3, 4.2%). The 3 metagenomic studies utilized the Illumina platform and internal, center-specific pipelines for pathogen identification; no other commercial platforms were reported [45, 76, 81]. Biospecimens tested varied widely and included blood, BALF, nasopharyngeal swabs, intra-abdominal samples, surgical site samples, and stool. BALF testing was performed in all lung transplant studies.

Although all studies (n = 72, 100%) reported percent pathogen detected, only 6 (8%) provided sensitivity, specificity, PPV, or NPV. Furthermore, while clinical course (n = 59, 82%), clinical outcomes (n = 44, 61%), and HCRU and cost (n = 19, 26%) were frequently reported (Figure 2*C*), only 6 studies (8%) directly assessed the impact of infection DT on clinical course (antimicrobials) or HCRU [56–58, 87, 95, 118].

Test Performance

Percent Pathogen Detected. Among the 45 studies using standard cultures, 39 reported culture yield, which was positive in a median of 27.7% (range, 0%–88.3%; Q1/Q3, 17.0%/49.6%) (Figure 3). Eleven studies evaluated blood cultures (median positive yield, 21.7%; range, 2.2%–55%) [61, 72, 73, 76, 77, 79, 82, 86, 92, 98, 110], and 5 evaluated BALF cultures (median positive yield, 36%; 5.3%–67%) [52, 53, 56, 57, 117].

Only 5 studies assessed pathogen yield for nonculture diagnostics (fungal biomarkers, n = 1; multiplex PCR, n = 3; metagenomic sequencing, n = 1), and primarily used culture as a comparator. In a study of lung transplant recipients, obtaining both standard culture and GM increased the diagnosis of invasive aspergillosis to 36%, compared with 23.3% and 16.1% for each test alone, respectively [52]. In a study of kidney transplant recipients with diarrhea, stool multiplex PCR outperformed microscopy and culture combined (yield 85% vs 32.3%, respectively) in detecting Norovirus, *Giardia lamblia*, *Cryptosporidium*, and enteropathogenic *Escherichia coli*, and others [103]. A multiplex PCR for bloodstream infections in heart or lung transplant recipients demonstrated 90.8% concordance with blood culture, with combined testing detecting pathogens in more specimens than blood culture alone (13.1% vs 6.1% of specimens tested, respectively) [116]. However, another multiplex PCR for suspected airway infections in lung transplant recipients failed to detect infections caused by pathogens not included in the platform, such as *Haemophilus parainfluenzae* and molds [57].

Of the 3 metagenomic testing studies, only one reported diagnostic yield: metagenomic sequencing of BALF from lung transplant recipients detected pathogens in 83.4% of cases versus 55.8% using CDM, which included culture (bacterial, mycobacterial, fungal), staining (fungal smear and Grocott's

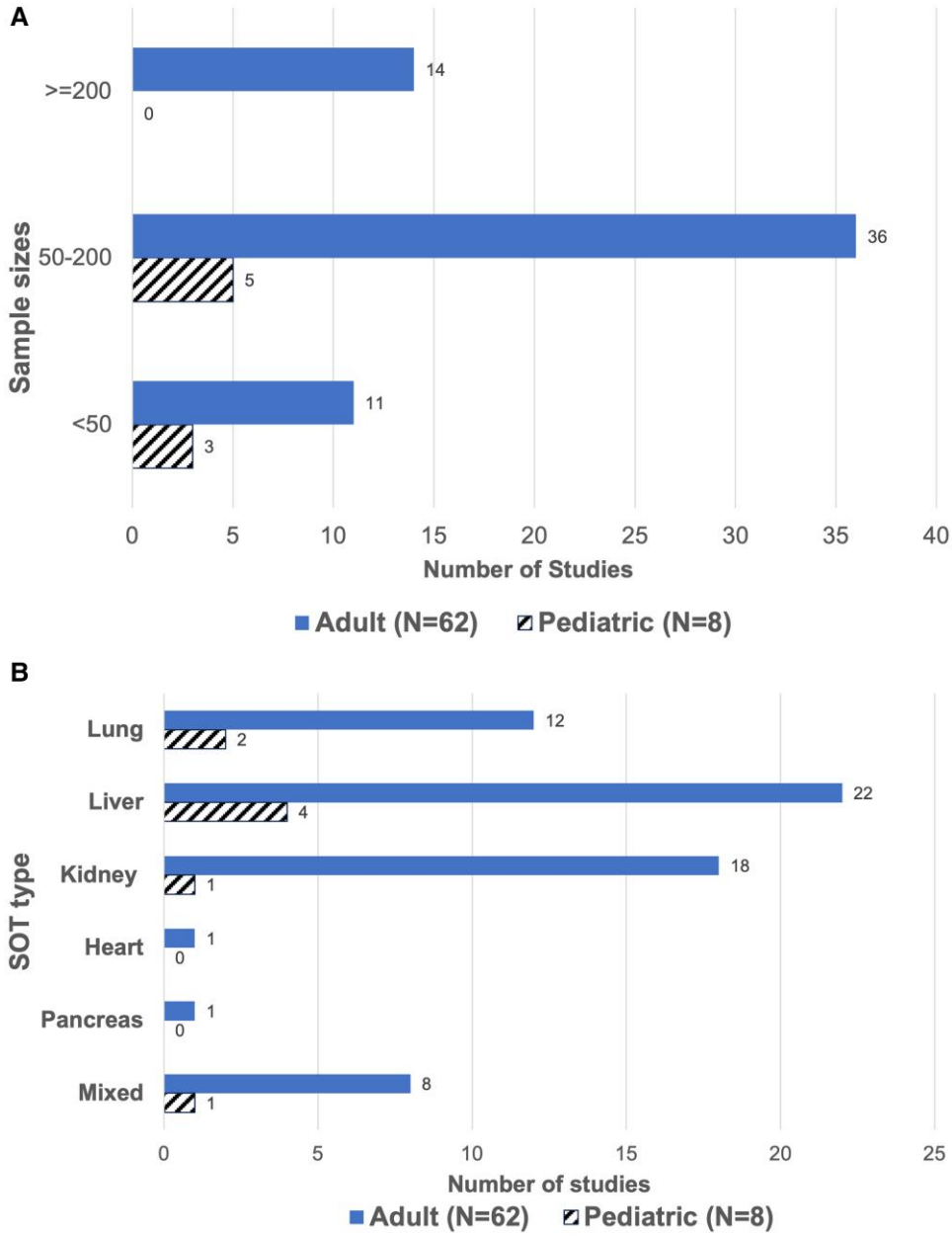

Figure 2. Characteristics of studies (pediatric N = 8; adult N = 64) included in the systematic literature review (SLR), 1 January 2012–11 June 2022. (*A*) Patient sample sizes for the studies included in the SLR. (*B*) Number of studies (pediatric and adult populations, respectively) for each solid organ transplant (SOT) type. (*C*) Number of studies by population and outcomes of interest identified in the SLR. Study references are listed in Supplementary Table 8.

methenamine staining [GMS]), PCR, serologies, and GM/BDG [45]. This approach led to antimicrobial changes in 21% (23/107) of cases, including infections with *Pneumocystis jirovecii* (not detected by GMS staining and not targeted by the PCR platform), *Mycobacteria* spp. (nontuberculous mycobacteria and *Mycobacterium tuberculosis*), *Legionella* spp., *Strongyloidiasis stercoralis*, and *Aspergillus* spp [45]. PCR later verified the 7 metagenomic tests that were positive for *P jirovecii*; GeneXpert MTB/RIF confirmed the 2 metagenomic tests showing *M tuberculosis*. However, cases with positive metagenomic sequencing results required adjudication by 2 expert clinicians to distinguish colonization from infection and to determine which pathogens were clinically relevant when results of metagenomic sequencing and CDM were discordant. Another study suggested that plasma metagenomic sequencing may complement culture for early detection of invasive fungal infection (IFI) following liver transplant, although diagnostic yield was not reported [76].

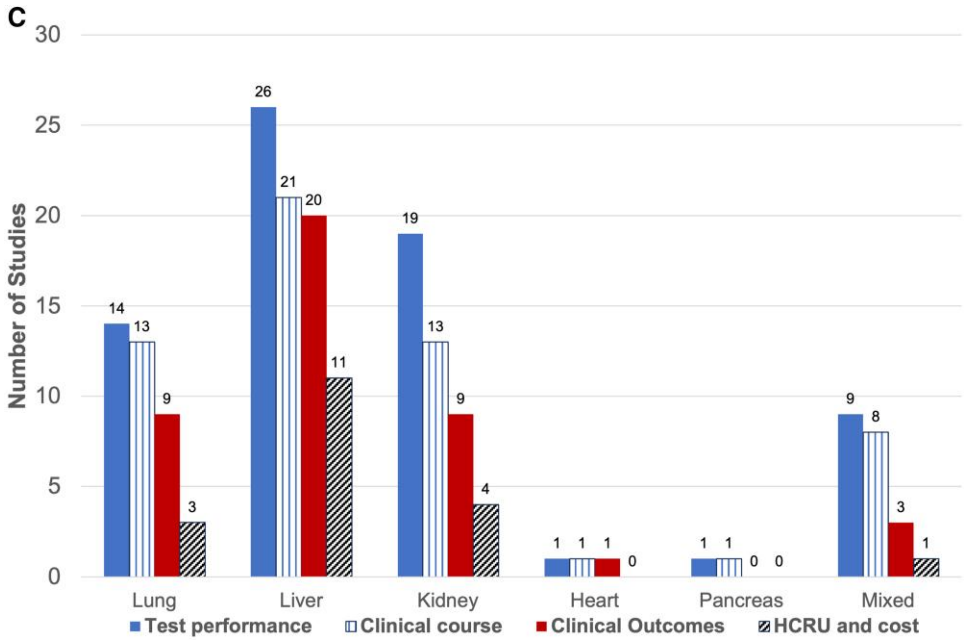

Figure 2. Continued

Test Accuracy. Sensitivity, specificity, PPV, and NPV were reported in 6 studies (Supplementary Table 9) [56–58, 87, 95, 118], evaluating biomarkers (BDG or CRP, n = 2) or PCR (n = 4). In a study primarily involving lung transplant recipients, BDG demonstrated low to moderate PPV for early IFI diagnosis (BALF, 26.2%; serum, 69.2%) [118]. Another study assessed CRP thresholds to predict bacterial infections following pediatric kidney transplant [87].

Four studies compared multiplex PCR assays with standard diagnostics in lung or kidney transplant recipients (Supplementary Table 9) [56–58, 95]. One study examined 7 commercial multiplex PCR assays in kidney transplant recipients with severe diarrhea [95]. Viral detection correlated well with reference methods, but detection of bacteria was potentially limited by poor specificity. For instance, molecular methods resulted in a 50% increase in detecting enteropathogenic *E coli* compared with stool culture, but the validity of these results could not be confirmed using reference methods [95]. Three studies assessed expanded multiplex PCR of BAL samples to diagnose lower respiratory infections in lung transplant recipients. Two were conducted in patients with suspected infection [56, 58], whereas 1 described patients undergoing routine surveillance [57]. Sensitivity varied depending on assay and pathogen, but PPV was generally high (Supplementary Table 9).

Turnaround Time. Five studies reported TAT, which was statistically significantly shorter for molecular compared with nonmolecular tests but also varied by test type. In lung transplant recipients, median TAT for multiplex bacterial PCR was 21.2 hours, compared with 23 hours for bacterial culture [56]. Similarly, multiplex PCR and directed RNA-viral PCR had TATs of 3.8 and 13 hours, respectively, versus 48 hours for bacterial culture [57]. Another study reported a median TAT of 2.3 hours for multiplex PCR versus 21.4–47.6 hours for usual care diagnostics, which included immunofluorescence and standard PCR [58]. In thoracic transplant recipients with suspected bloodstream infections, PCR results were available 1.5 days earlier than blood cultures [116]. Metagenomic sequencing also had a significantly shorter TAT than CDM in lung transplant recipients with various infections (2.7 vs 5.5 days, respectively) [45]. No studies reported TAT for other DTs.

Clinical Course

Clinical course (primarily antimicrobial use) was reported in 59 studies, although only 4 specifically evaluated the impact of infection DT on antimicrobial-related decisions. In 1 study of 50 pediatric liver transplant recipients undergoing 157 percutaneous cholangiography procedures, prophylactic antimicrobials were administered universally and continued in 73.2% (115/157) of procedures due to cholangitis, sepsis, or colonization with drug-resistant pathogens [61]. However, in 12% (14/115) of these cases, antimicrobials were optimized based on positive blood or biliary cultures [61]. In 3 studies of lung transplant recipients, antimicrobial modification or discontinuation followed multiplex PCR [57], GM [52], and/or culture [50, 57] of respiratory samples.

Table 1. Diagnostic Tools Utilized in Studies by SOT Type

Test type		SOT Type						
		Liver	Lung	Kidney	Mixed	Heart	Pancreas
Culture	n	21	4	16	8	1	1
	reference	[57, 65–70, 72–80, 82–84] and [61–64][a]	[45, 51, 53, 54, 60]	[88–94, 96–103, 105, 106] and [87][a]	[110–112, 114–118] and [109][a]	[107]	[108]
Biomarkers, antigens (type, if specified)	n	1	2	2	1	NS	NS
	reference	[76] (BDG, GM, cytokines)	[52, 55] (GM)	[96] (GM, BDG) [87][a] (CRP, WBC, ANC)	[109][a] (viral antigen)		
Serology	n	1	NS	4	3	1	NS
	reference	[62][a]		[88, 90, 96] and [87][a]	[113, 115, 116]	[107]	
PCR (eg, multiplex)	n	3	6	6	3	1	NS
	reference	[57, 71, 86] and [62][a]	[50, 56, 58, 59] and [48, 49][a]	[90, 95, 96, 103, 104] and [87][a]	[113, 115, 116]	[107]	
16S rRNA sequencing	n	1	NS	NS	NS	NS	NS
	reference	[85]					
Metagenomic sequencing	n	2	1	NS	NS	NS	NS
	reference	[76, 81]	[45]				

Data yielded from systematic literature review, 1 January 2012–11 June 2022. Tests reported utilized in a study are noted, although studies may have provided limited data regarding specific test results or performance or commented on findings based on a compilation of results from multiple test types.

Abbreviations: ANC, absolute neutrophil counts; BAL, bronchoalveolar lavage; BDG, (1→3)-β-D-glucan; CRP, C-reactive protein; GM, Galactomannan; NS, no studies reported; PCR, polymerase chain reaction; SOT, solid organ transplant; WBC, white blood cells.

[a]Pediatric (≤18 y) studies.

Clinical Outcome, HCRU, and Cost

Mortality was reported in all 44 studies that described clinical outcomes. However, none evaluated the direct impact of infection DT results on mortality, and reporting methods varied (eg, different follow-up durations posttransplant). Median all-cause mortality (ie, including but not limited to infections) posttransplant was 15.2% (range, 0%–80%; Q1/Q3, 6.8%/27.2%). Eighteen studies reported all-cause mortality rates >20% [51, 53, 54, 56, 65, 66, 71, 74, 76, 79, 80, 86, 96, 102, 107, 109, 112, 117]. Graft loss was reported in 4 studies, [89, 97, 102, 106] but none explored potential relationships between graft loss, DT results, and antimicrobials.

Eighteen studies reported HCRU outcomes (Figure 2*C*), including hospital length of stay (LOS; n = 16) [53, 55, 62, 63, 70, 75–77, 81, 89–91, 95, 96, 111, 112], intensive care unit admission (n = 2), [59, 95] and intensive care unit LOS (n = 9) [53, 63, 65, 70, 74, 76, 77, 80, 86]. However, none directly assessed the influence of positive DT results on HCRU because positive results served as a proxy for infection. No studies reported cost.

DISCUSSION

This SLR of 72 studies evaluating infection DT in SOTR identified several key findings. First, significant heterogeneity existed across studies, which varied in design, SOTR populations, infections, DT methods, and specimens tested. Second, while most studies evaluated cultures, and some included PCR assays, novel MDT like BRPCR and metagenomics were rarely examined. Third, despite faster TATs, PCR tests were limited by their fixed array of detectable organisms. Although BRPCR and metagenomics could overcome this limitation, data on these MDT were scarce. Fourth, only 6 studies reported sensitivity, specificity, PPV, and NPV. Finally, few studies reported the impact of infection DT on clinically relevant outcomes like antimicrobial use, mortality, LOS, HCRU, and cost. These findings highlight significant knowledge gaps in infection DT for SOTR, underscoring the need for prospective studies to evaluate the performance and clinical impact of advanced MDT compared with conventional DT methods in SOTR.

Diagnosing infections in SOTR typically involves a stepwise approach [22], starting with basic microbiological assessment and consideration of empiric antimicrobials, followed by more extensive testing and changes in antimicrobial therapy if the patient deteriorates or opportunistic infection is suspected. The diagnostic journey often includes a combination of modalities such as imaging, cultures, antigen tests, serology, and PCR, with advanced pathogen-agnostic diagnostics like BRPCR and metagenomics reserved as last resort measures. A paradigm shift toward earlier use of pathogen-agnostic diagnostics in SOTR is appealing because such approaches could potentially help overcome cognitive biases and facilitate timely

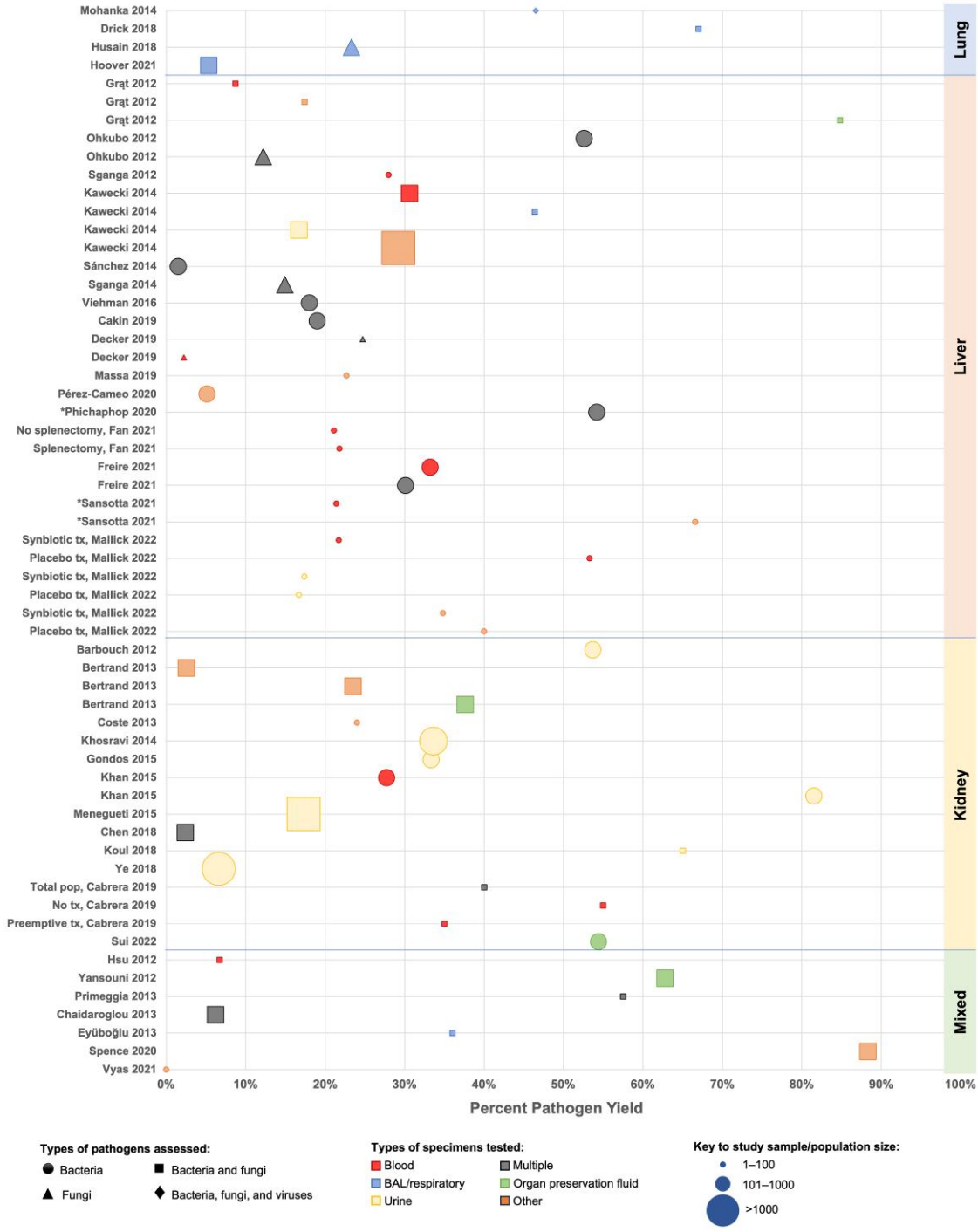

Figure 3. Reported pathogen positivity from culture in studies of patients by transplant type. Data yielded from systematic literature review, 1 January 2012–11 June 2022. Percent pathogen detected from culture based on specimen type is indicated on the X-axis for each study reporting these data. Study sample or population size, as relevant, range from 23 to 1307. Marker sizes correspond to the study sample or population size: small, 1–100; medium, 101–1000; large, >1000. Data from pediatric (defined as aged less than 18 y) studies are denoted by an asterisk (*) next to the study author. "Multiple" in specimen types represents an aggregate of 2 or more specimens used for testing, and "Other" indicates a sample other than blood, respiratory, urine, or organ preservation fluid (eg, stool, rectal swab, intra-abdominal fluid, bile, surgical site). Abbreviations: BAL, bronchoalveolar lavage; pop, population; tx, therapy.

treatment of fastidious organisms. However, our data indicate that advanced pathogen-agnostic diagnostics require additional validation. Indeed, despite growing interest, research on these novel DT modalities in SOTR remains limited [119, 120]. This paradox—frequent clinical use despite limited supporting evidence—was highlighted by the American Society of

Transplantation [121]. Furthermore, we identified no cost-effectiveness analyses to determine whether the increased cost of pathogen-agnostic MDTs can be offset by other cost savings, for instance from a reduction in the total number of tests ordered; we also identified no studies evaluating the cost of combining multifaceted diagnostic approaches (eg, culture, antigens, histology, PCR, either sequentially or simultaneously).

While BDG and GM assays were designed to rapidly diagnose IFI, few studies have examined their performance in SOTR. BDG has poor specificity, cannot identify specific fungi, and can yield false positives [14, 22, 122]. Although serum GM is accurate in neutropenic cancer patients (70–82% sensitivity, 86–92% specificity), it is less sensitive in SOTR (22% sensitivity, 84% specificity) [24]. Thus, a negative serum GM result cannot exclude invasive aspergillosis in SOTR with lung nodules [24]. Conversely, BAL GM has >80–90% sensitivity and specificity in both neutropenia and SOTR [24]. No studies evaluated antigen-based biomarkers for endemic mycoses or *Cryptococcus* in SOTR. Fungal antigen tests also exhibit cross-reactivity, and no commercial antigen tests exist for resistant mycoses like Mucorales and *Scedosporium* [24]. While PCR assays for these molds exist [123, 124], we identified no studies focused solely on SOTR. One study with ∼25% SOTR found that serum *Mucorales* PCR identified mucormycosis earlier than CDM (primarily histopathology), leading to earlier treatment with amphotericin B and improved survival [125]. However, pathogen-directed PCR requires clinicians to suspect the specific pathogen. Whether pathogen-agnostic MDT will outperform conventional methods and PCR for diagnosing IFI remains unknown, highlighting the need for further study and for proper diagnostic stewardship.

Ju et al evaluated the utility of pathogen-agnostic MDT for diagnosing *P jirovecii* pneumonia (PJP) in lung transplant recipients [45] and highlight important considerations for rational use of metagenomics-based DT. GMS staining, a conventional and commonly used test for PJP despite its poor sensitivity in persons without HIV [126], missed all 7 PJP cases, and the PCR assay used was not designed to detect *P jirovecii*. The diagnosis of PJP was made through metagenomic sequencing and subsequently verified by a *P jirovecii*–specific PCR. Importantly, clinical adjudication confirmed that all 7 of these cases were consistent with PJP, underscoring the critical role of clinical judgment, which should never be replaced by DT results. This is particularly true for pathogens such as *P jirovecii*, where DNA detection may indicate colonization not disease [127]. Rational interpretation of metagenomic tests requires nuanced clinical expertise to avoid reflexive interpretation of results. However, such expertise may not be readily available. Whether genome copies or cycle threshold values can further refine medical decision-making in patients with positive metagenomic testing results remains to be determined [127].

Although PCR can accurately diagnose CMV and EBV infection after SOT [128, 129], diagnosing other DNA viruses remains challenging. We identified no studies focused on this issue. For example, diagnosing HHV-8 after SOT is difficult because of low clinical suspicion and limited commercial assays with variable turnaround times, despite the increasing incidence of donor-derived HHV-8 [9, 130]. A recent study using plasma microbial cell-free DNA (mcfDNA) sequencing to monitor for infections after lung transplant identified one case where HHV-8 was detected in posttransplant plasma samples. This individual, whose pretransplant sample was negative for HHV-8, subsequently developed disseminated Kaposi sarcoma with allograft involvement, which was diagnosed on autopsy and strongly suggested DDI [131]. Such data remain anecdotal, and whether pathogen-agnostic testing will have a role in DDI surveillance remains unknown but should be studied. Diagnosing rare CNS viruses like HHV-6 and JC after SOT is also challenging [132] and relies on a high index of suspicion. We identified no studies evaluating novel DT for these viruses in SOT.

Metagenomic sequencing holds promise for diagnosing infections in immunocompromised patients but requires further validation. Bergin et al [44] showed that in patients with hematologic malignancies and suspected infectious pneumonia, combining mcfDNA sequencing with usual care testing improved the infectious diagnostic yield to 42% (from 30% and 28%, respectively). Plasma mcfDNA sequencing alone provided an additive diagnostic value of 12%, detecting *P jirovecii*, rare molds, *Nocardi,* and others. mcfDNA sequencing also detected organisms often dismissed as commensals but which can cause disease in hematological cancer. Importantly, an expert committee adjudicated the significance of all microbes detected. However, this study also revealed limitations of plasma mcfDNA sequencing. The proportion of plasma mcfDNA tests yielding the same pathogen as usual care was highest for DNA viruses and bacteria but lowest for *Aspergillus*. Most cases of pulmonary aspergillosis were diagnosed exclusively because of compatible imaging and a positive serum GM result, but plasma mcfDNA results were negative in nearly all these cases. Potential causes of false-negative metagenomics testing results include low pathogen DNA concentrations or thick fungal cell walls [133]. Another study in hematopoietic cell transplant recipients showed that mcfDNA sequencing had variable sensitivity for detecting different mold species, with improved performance for non-*Aspergillus* molds and in early samples [134].

Importantly, in the study by Bergin et al [44] ∼58% of participants lacked a microbiologically confirmed cause of their pulmonary process. Whether these cases are “false negatives” or “true negatives” is currently difficult to determine definitively but is an important research question. Because individuals with a confirmed diagnosis (infectious or otherwise) were

excluded, the study may have included many participants with (1) difficult-to-diagnose infections (in whom the negative DT results are false negatives) or (2) a noninfectious etiology of their pulmonary process (in whom the negative DT results are true negatives); this premise should be explored in future studies. Finally, current tests may miss some pathogens, particularly RNA viruses, which may not be included in certain testing platforms [135]. Ultimately, further refinement of diagnostic technologies is needed. Clinicians using pathogen-agnostic MDT must interpret results (both positive and negative) cautiously and in the context of the patient's clinical presentation. Transplant centers adopting such technologies should develop algorithms for rational use and employ diagnostic stewardship with infectious disease expertise.

Study Limitations

This SLR, although conducted using established guidelines, has limitations. Search criteria may have been too restrictive or did not match selected MeSH terms, despite a supplemental manual search. The included studies (N = 72) were of varied quality, including retrospective and noncomparative designs. While our exclusion criteria encompassed studies evaluating only a single pathogen or exclusively RNA viruses, all such studies (N = 13 and N = 3, respectively) were also excluded for other reasons, including not addressing the research question (Supplementary Tables 5 and 6). Notably, studies evaluating RNA viruses alongside other pathogens were still included [48–50, 57–59, 95, 96, 103, 104, 113]. Variability in diagnostic approaches reflects the diverse clinical practices and DT access across different regions and institutions. Heterogeneity in the "gold" standard complicates interpreting test performance across studies. This review focused on hospitalized patients and did not evaluate diagnostics for unrecognized donor-derived infection. Thus, findings cannot be generalized to all SOTR or diagnostic approaches.

CONCLUSION

This SLR reveals a critical gap: although noninvasive monitoring for allograft rejection has progressed [136–138], the development of advanced molecular diagnostics for infection in SOTR lags behind. However, transplant clinicians frequently use novel infectious DT [121], despite limited supporting evidence. Thus, future prospective studies must prioritize evaluating the performance and clinical impact of novel tests like metagenomic sequencing and broad-range PCR following transplantation. Study endpoints should include diagnostic accuracy, antimicrobial use, mortality, healthcare resource utilization, and cost. Novel molecular diagnostic tests should be studied in the context of donor-derived infections. Finally, clinicians and medical centers should recognize the critical role of diagnostic stewardship and clinical expertise in interpreting the results of novel molecular diagnostics.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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