VRAAG 1: HOE KAN ONDERSCHEID WORDEN GEMAAKT TUSSEN KOORTS DOOR INFECTIES OF TUMORKOORTS?

Primaire studies

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
Al Shuaibi 2013	• Design: retrospective cohort study • Funding: not reported; CoI: none • Setting: single university centre, US • Sample size: N=340 • Duration: recruitment Jun 2009 – Dec 2010	• Eligibility criteria: febrile consecutive patients with hematologic malignancy • Exclusion criteria: critically ill patients admitted to the ICU • *A priori* patient characteristics: ○ M/F: 190/150 ○ Median age: 59y ○ Cancer type: AML N=142, lymphoma N=71	Diagnostic test(s): Procalcitonin at onset of fever and during follow-up 4-7d later Reference standard: Physical examination, laboratory studies, microbiology, response to antibiotics Target disorder: Bacterial infections vs. no infections	CRITICAL OUTCOMES • AUC: 0.5417 (95%CI 0.4774-0.6060)	Level of evidence: unclear risk of bias • Consecutive patients, but otherwise unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Chang 1984	• Design: cohort study • Funding: supported in part by the Oncology Research Grant of the Good Samaritan Foundation, Dayton, Ohio; CoI: not reported • Setting: single centre, US • Sample size: N=22 • Duration: unclear	• Eligibility criteria: patients with cancer or suspected malignancy and fever (at least once >101° F) of undetermined origin for more than 7 days; no evidence of infection on careful physical examination, negative results of adequate blood and urine cultures, absence of pneumonia on chest roentgenography, normal findings in spinal fluid in patients who underwent spinal puncture, lack of evidence of drug fever • *A priori* patient characteristics: ○ M/F: 11/11 ○ Age range: 28-73y ○ Cancer type: acute leukemia N=4, colon cancer N=4, CLL stage 3-4 N=3	Diagnostic test(s): Adequate treatment with Naproxen 2x250 mg/day, defined as a course of therapy for at least 3 days and complete lysis of fever to <99° F within 24 hours after the initiation of naproxen and sustained normal temperature for more than 5 days while receiving the drug Reference standard: Physical examination and laboratory studies Target disorder: Neoplastic fever	CRITICAL OUTCOMES • Sensitivity: 93% • Specificity: 100% • PPV: 100% • NPV: 88%	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification • 15 patients were initially treated with adequate courses of antibiotics and none had any significant response to treatment; treatment with naproxen was therefore initiated • 7 patients initially received naproxen alone because they were strongly suspected to have neoplastic fever
Chang 1987	• Design: cohort study • Funding: unclear; CoI: unclear • Setting: single centre, US	• Eligibility criteria: not reported • Exclusion criteria: not reported • *A priori* patient characteristics: not reported	Diagnostic test(s): Adequate treatment with Naproxen 2x250 mg/day, defined as a course of therapy for at least 3 days and	CRITICAL OUTCOMES • Sensitivity: 92% • Specificity: 100% • PPV: 100% • NPV: 82%	Level of evidence: unclear risk of bias • Poorly reported study • Possible overlap with Chang 1984

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Sample size: N=62, with 68 FUO events • Duration: unclear		complete lysis of fever to <99° F within 12 hours after the initiation of naproxen and sustained normal temperature for more than 3 days while receiving the drug Reference standard: Not reported Target disorder: Neoplastic fever		• Diagnostic accuracy reported on the level of FUO events
Debiane 2014	• Design: prospective cohort study • Funding: supported, in part, by institutional funds/PCT provided by Thermo-Fischer; CoI: one author who received support • Setting: single university centre, US • Sample size: N=114 • Duration: unclear	• Eligibility criteria: critically ill patients with cancer, 18y and older, who were febrile at admission to the ICU or became febrile during the course of their stay in the ICU • Exclusion criteria: patients with medullary thyroid carcinoma and patients with small cell carcinoma • *A priori* patient characteristics: ○ M/F: 67/47 ○ Median age: 57y ○ Cancer type: hematologic N=55, solid tumour N=59	Diagnostic test(s): Procalcitonin and CRP within 24h of onset of fever and during follow-up 4-7d later Reference standard: Physical examination, microbiology, response to antibiotics Target disorder: Sepsis and bloodstream infections	CRITICAL OUTCOMES • Procalcitonin: optimal cut-off 1.9 ng/ml for diagnosis of bloodstream infections: ○ Sensitivity: 67% (95%CI 49-84%) ○ Specificity: 72% (63-82%) ○ PPV: 43% (28-58%); highest PPV = 48% with cut-off of 6.0 ng/ml ○ NPV: 88% (80-95%); highest NPV = 93% with cut-off of 0.5 ng/ml ○ AUC: 0.7132 (0.60-0.83) • CRP: diagnosis of bloodstream infections ○ AUC: 0.5261 (0.39-0.66; p=0.003 vs. procalcitonin)	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Diness 2014	• Design: prospective cohort study • Funding: unclear; CoI: not accessible • Setting: single centre, Denmark • Sample size: N=41 • Duration: recruitment May 2011 – May 2012	• Eligibility criteria: patients hospitalised due to fever or clinical signs of infection were included upon admission to the Department of Oncology • *A priori* patient characteristics: infection vs. no infection ○ M/F: 13/12 vs. 8/8 ○ Median age: 66 vs. 68.5y ○ Cancer type: gastrointestinal N=13, lung N=9, urogenital N=9, breast N=8, head/neck N=2	Diagnostic test(s): Procalcitonin and CRP on day 1-3 Reference standard: Clinical, microbiological and radiological data Target disorder: Infection vs. no infection	CRITICAL OUTCOMES • Procalcitonin: cut-off 0.5 µg/l, detection of infection ○ Sensitivity: 56% ○ Specificity: 88% ○ PPV: 88% ○ NPV: 56% ○ AUC: 0.836 (95%CI 0.735-0.937) • CRP: cut-off 50 µg/l, detection of infection ○ Sensitivity: 92% ○ Specificity: 31% ○ PPV: 68% ○ NPV: 71% ○ AUC: 0.847 (0.754-0.940)	Level of evidence: unclear risk of bias • 10/51 originally included patients never had procalcitonin evaluated and were therefore excluded • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Ding 2020	• Design: retrospective cohort study • Funding: supported by the Shandong Provincial Key Research and	• Eligibility criteria: patients with nonneutropenic lung cancer with fever	Diagnostic test(s): Procalcitonin and CRP within 48h of the onset of fever	CRITICAL OUTCOMES • Procalcitonin: cut-off 0.105 ng/ml, detection of bacterial infection ○ Sensitivity: 79.7%	Level of evidence: unclear risk of bias

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	Development Program (2017CXGC1207 and 2016GSF201162), Jinan Clinical Medical Science and Technology Innovation Program (201704080), Wu Jieping Medical Fund (no. 320.6750.19088-24); CoI: none • Setting: single centre, China • Sample size: N=125 • Duration: recruitment Jan 2019 – Dec 2019	• *A priori* patient characteristics: not reported separately for subset	Reference standard: Clinical, microbiological, and radiological data Target disorder: Bacterial infection vs. neoplastic fever	○ Specificity: 80.4% ○ PPV: 83.3% ○ NPV: 76.3% ○ AUC: 0.874 (95%CI 0.813-0.935) • CRP: cut-off 12.2 mg/l, detection of bacterial infection ○ Sensitivity: 85.5% ○ Specificity: 71.4% ○ PPV: 78.7% ○ NPV: 80.0% ○ AUC: 0.855 (0.790-0.919)	• Subset of 125/588 patients were included in this analysis • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Ebihara 2017	• Design: retrospective cohort study • Funding: supported in part by Grants-in-Aid for Scientific Research from the Japanese Ministry of Education, Culture, Sport, Science, and Technology (JSPS KAKENHI # 26461431) and by the National Cancer Center Research and Development Fund (26-A-24) to N.A.; CoI: not reported • Setting: single university centre, Japan • Sample size: N=28 with 49 febrile episodes • Duration: recruitment Mar 2014 – Mar 2016	• Eligibility criteria: patients with hematologic malignancy and admitted to receive chemotherapy and/or HSCT; procalcitonin and CRP levels were measured simultaneously within 72 hours after each febrile episode; estimated glomerular filtration rate >60 mL/min/m^2 • *A priori* patient characteristics: ○ M/F: 19/9 ○ Median age: 50y ○ Cancer type: leukemia N=19, lymphoma N=5, myelodysplastic syndrome N=4	Diagnostic test(s): Procalcitonin and CRP within 72 hours of the onset of fever Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. no infection	CRITICAL OUTCOMES • AUC: procalcitonin 0.753 (95%CI 0.6151-0.89), CRP 0.453 (0.2856-0.6213)	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification • Analysis on the level of febrile episode
Hangai 2015	• Design: retrospective cohort study • Funding: not reported; CoI: not accessible • Setting: single university centre, Japan • Sample size: N=91 fever episodes • Duration: unclear	• Eligibility criteria: patients who were planned for treatment of de novo or relapsed acute lymphoblastic leukemia, non-Hodgkin lymphoma, Hodgkin lymphoma or multiple myeloma; fever, defined as axillary temperature >37.5° C • *A priori* patient characteristics: ○ M/F: 53/38	Diagnostic test(s): Procalcitonin and CRP within 3 days after the onset of fever Reference standard: Clinical, radiological, and microbiological data Target disorder:	CRITICAL OUTCOMES • Procalcitonin: cut-off 0.27 ng/ml, detection of infection ○ Sensitivity: 50.0% ○ Specificity: 82.1% ○ PPV: 65.0% ○ NPV: 71.1% ○ AUC: 0.697 • CRP: cut-off 5.4 mg/dl, detection of infection ○ Sensitivity: 74.4%	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
			Neoplastic fever vs. infection	○ Specificity: 57.7% ○ PPV: 72.5% ○ NPV: 60.0% ○ AUC: 0.670	
Jabbour 2022 EXCLUSION: only data on distinction between gram-negative blood stream infections and all other fever etiologies	• Design: prospective cohort study • Funding: not reported; CoI: none • Setting: single university centre, Italy • Sample size: N=217 with 286 febrile episodes • Duration: …	• Eligibility criteria: patients with hematological diseases and fever, and older than 18 years • *A priori* patient characteristics: ○ M/F: 120/97 ○ Median age: 70y ○ Cancer type: NHL N=78, AML N=50, myelodysplastic syndrome N=24	Diagnostic test(s): Procalcitonin and CRP Reference standard: Clinical, radiological, and microbiological data Target disorder:	CRITICAL OUTCOMES • Sensitivity: • Specificity: • PPV: • NPV: • AUC:	Level of evidence: … risk of bias • PCT and CRP results were blinded
Kallio 2001 Kallio 2000	• Design: prospective cohort study • Funding: not reported; CoI: not reported • Setting: single university centre, Finland • Sample size: N=66 • Duration: recruitment Sep 1996 – Mar 1998	• Eligibility criteria: cancer patients with clinically suspected infection and with Karnofsky performance scores higher than 40 • Exclusion criteria: no criteria met for infection or neoplastic fever • *A priori* patient characteristics: ○ M/F: 41/25 ○ Mean age: infection 57y, neoplastic fever 61y ○ Cancer type: lymphoma N=25, lung cancer N=12, gastrointestinal tract N=8, breast cancer N=7	Diagnostic test(s): CRP on day 0, 3 and 5, ESR at entry, and procalcitonin Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. neoplastic fever	CRITICAL OUTCOMES • Procalcitonin: cut-off 0.24 ng/ml, detection of infection ○ Sensitivity: 59% (95%CI 45-72) ○ Specificity: 70% (35-93) ○ PPV: 92% (78-98) ○ NPV: 23% (10-42) ○ AUC: 0.61 (95%CI 0.42-0.81) • CRP: cut-off 140 mg/l, detection of infection ○ Sensitivity: 39% (27-53) ○ Specificity: 70% (35-93) ○ PPV: 88% (69-98) ○ NPV: 17% (7-32) ○ AUC: 0.42 (95%CI 0.28-0.57) • ESR: ○ AUC: 0.27 (0.14-0.41)	Level of evidence: unclear risk of bias • 92 consecutive patients, 26 excluded because they had simultaneous antibiotics and cancer treatments • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Mori 2011	• Design: retrospective cohort study • Funding: supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology in Japan; CoI: none • Setting: single university centre, Japan • Sample size: N=77 with 144 febrile episodes • Duration: recruitment Dec 2009 – Jul 2010	• Eligibility criteria: patients with hematological malignancies or aplastic anemia on anticancer chemotherapy or immunosuppressive therapy, who developed febrile episodes • *A priori* patient characteristics: on the level of febrile episode ○ M/F: 74/70 ○ Median age: 54y ○ Cancer type: lymphoma N=62, myelodysplastic syndrome / AML N=51	Diagnostic test(s): Procalcitonin and CRP within 24h after onset of fever Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. no infection	CRITICAL OUTCOMES Non-HSCT patients • Procalcitonin: detection of infection ○ Sensitivity: 33.3% ○ Specificity: 92.6% ○ PPV: 90.9% ○ NPV: 38.5% • CRP: cut-off 2.5 mg/dl, detection of infection ○ Sensitivity: 76.7% ○ Specificity: 48.1% ○ PPV: 76.7% ○ NPV: 48.1% HSCT patients • Procalcitonin: detection of infection ○ Sensitivity: 63.6%	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification • Analysis on the level of febrile episodes

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
				○ Specificity: 68.6% ○ PPV: 56.0% ○ NPV: 75.0% • CRP: cut-off 9.5 mg/dl, detection of infection ○ Sensitivity: 50.0% ○ Specificity: 88.6% ○ PPV: 73.3% ○ NPV: 73.8%	
Penel 2004	• Design: retrospective cohort study • Funding: not reported; CoI: not reported • Setting: single university centre, France • Sample size: N=155 • Duration: recruitment Jan – Dec 2002	• Eligibility criteria: cancer patients with febrile episodes • *A priori* patient characteristics: not provided for the 155 cases separately	Diagnostic test(s): Procalcitonin and CRP Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. neoplastic fever	CRITICAL OUTCOMES • Procalcitonin: cut-off 2 ng/ml, detection of infection ○ Sensitivity: 17% ○ Specificity: 95% ○ PPV: 90% ○ NPV: 29%	Level of evidence: high risk of bias • 252 consecutive admissions: 7 excluded because of concomitant diagnosis of infection and paraneoplastic fever; 155 cases were included for the CRP and procalcitonin analyses • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification • 2x2 tables only provided for procalcitonin
Rao 2022	• Design: retrospective cohort study • Funding: supported by the Key R&D Project of Sichuan Provincial Department of Science and Technology (Grant numbers [2022ZYF1927]) and the Key R&D Project of Chengdu Science and Technology Bureau (Grant numbers [YF05-01792-SN]); CoI: none • Setting: single university centre, China • Sample size: N=102 • Duration: recruitment Jul 2019 – Aug 2021	• Eligibility criteria: adult cancer patients whose body temperature was greater than 38 ˚C on the day of admission • Exclusion criteria: patients diagnosed with leukemia, medullary thyroid carcinoma, or small cell lung carcinoma; patients that used antibiotics within 4 weeks • *A priori* patient characteristics: infection vs. no infection ○ M/F: 41/31 vs. 18/12 ○ Mean age: 57 vs. 54y ○ Cancer type: lung N=23, cervical N=19, lymphoma N=14	Diagnostic test(s): Procalcitonin and CRP Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. no infection	CRITICAL OUTCOMES • Procalcitonin: cut-off 0.69 ng/ml, detection of infection ○ Sensitivity: 56.94% ○ Specificity: 96.67% ○ PPV: 97.6% ○ NPV: 48.3% ○ AUC: 0.769 (95%CI 0.681-0.857) • CRP: cut-off 64.81 mg/l, detection of infection ○ Sensitivity: 65.28% ○ Specificity: 66.67% ○ PPV: 82.5% ○ NPV: 44.4% ○ AUC: 0.664 (95%CI 0.554-0.775)	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Schuttrumpf 2003	• Design: prospective cohort study • Funding: not reported; CoI: not reported	• Eligibility criteria: patients with hematological and oncological diseases presenting with fever • *A priori* patient characteristics:	Diagnostic test(s): Procalcitonin and CRP Reference standard:	CRITICAL OUTCOMES • Procalcitonin: cut-off 0.2 μg/l ○ Sensitivity: 87.5%	Level of evidence: unclear risk of bias • Consecutive patients

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: single university centre, Germany • Sample size: N=95 • Duration: recruitment Jun 2000 – Aug 2001	○ M/F: 52/43 ○ Median age: 53y ○ Cancer type: AML N=47, NHL N=21	Clinical, radiological, and microbiological data Target disorder: Neoplastic fever vs. infection	○ Specificity: 80.8% ○ NPV: 98.4% • CRP: cut-off 119 mg/l ○ Sensitivity: 87.5% ○ Specificity: 42.3%	• Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Shen 2020	• Design: retrospective cohort study • Funding: not reported; CoI: none • Setting: single centre, China • Sample size: N=119 • Duration: recruitment May 2018 – Feb 2020	• Eligibility criteria: patients with gynecological malignant tumors and fever • Exclusion criteria: patients aged <18 years old; those who died within 24 hours of enrollment; patients with agranulocytosis (<0.5×10^9/L); patients with HIV infection, type 2 diabetes, viral hepatitis, and autoimmune diseases; patients with blood bacterial culture results suspected of contamination; non-gynecological malignant tumor patients; mental illness patients; and fever patients induced by non-infectious factors such as allergic reactions, chemotherapy drugs or blood products • *A priori* patient characteristics: ○ M/F: 0/119 ○ Age range: 34-71 ○ Cancer type: ovarian N=37, cervical N=43, endometrial N=39	Diagnostic test(s): Procalcitonin and CRP Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. no infection	CRITICAL OUTCOMES • Procalcitonin: cut-off 10.4 ng/ml, detection of infection ○ Sensitivity: 70.3% ○ Specificity: 74.5% ○ AUC: 0.74 (95%CI 0.65-0.83) • CRP: cut-off 61.42 mg/l, detection of infection ○ Sensitivity: 90.6% ○ Specificity: 56.4% ○ AUC: 0.818 (95%CI 0.743-0.893)	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Shomali 2012 EXCLUSION: only diagnostic accuracy data on distinction between blood stream infections and all other fever etiologies	• Design: retrospective cohort study • Funding: none; CoI: none • Setting: single university centre, US • Sample size: N=248 • Duration: unclear	• Eligibility criteria: non-neutropenic febrile cancer patients • *A priori* patient characteristics: ○ M/F: 142/106 ○ Median age: 56y ○ Cancer type: gastrointestinal N=67, genitourinary N=41, lymphoma N=33	Diagnostic test(s): Procalcitonin Reference standard: Clinical, radiological, and microbiological data, or response to Naproxen test Target disorder:	CRITICAL OUTCOMES • Sensitivity: • Specificity: • PPV: • NPV: ○ AUC:	Level of evidence: … risk of bias • …
Vassallo 2021	• Design: retrospective cohort study • Funding: not reported; CoI: not reported	• Eligibility criteria: patients with solid tumors admitted for fever • *A priori* patient characteristics: ○ M/F: 88/43	Diagnostic test(s): Procalcitonin Reference standard:	CRITICAL OUTCOMES Cut-off 0.52 ng/ml: • Sensitivity: 75%	Level of evidence: unclear risk of bias • Unclear selection process

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
	• Setting: single centre, France • Sample size: N=131 • Duration: recruitment Jan 2015 – Nov 2019	○ Mean age: 67.9y ○ Cancer type: genitourinary N=28, colorectal N=25, Other gastrointestinal N=23	Clinical, radiological, and microbiological data Target disorder: Infection-related vs. tumor-related fever	• Specificity: 55% • PPV: 77% • NPV: 52%	• Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Vincenzi 2016	• Design: retrospective cohort study • Funding: not reported; CoI: none • Setting: single university centre, Italy • Sample size: N=431 • Duration: recruitment Jan 2009 – Mar 2013	• Eligibility criteria: patients with known diagnosis of solid metastatic or locally advanced tumor (not operable) and fever • Exclusion criteria: previous antibiotic treatment started within 4 weeks before hospital admission • *A priori* patient characteristics: ○ M/F: 235/196 ○ Age: 18-60y N=149, 61-70y N=126, >70y N=156 ○ Cancer type: colorectal cancer N=80, other gastrointestinal N=93, thoracic N=65, genitourinary N=63	Diagnostic test(s): Procalcitonin Reference standard: Hemoculture Target disorder: Positive vs. negative hemoculture	CRITICAL OUTCOMES Cut-off 1.52 ng/dl: • Sensitivity: 61.6% • Specificity: 70.1% • PPV: 30.4% • AUC: 0.7	Level of evidence: unclear risk of bias • Consecutive patients • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification
Wang 2017	• Design: prospective cohort study • Funding: none; CoI: none • Setting: 2 centres, Singapore • Sample size: N=80 with 108 cases of fever • Duration: recruitment Aug 2014 – Nov 2015	• Eligibility criteria: patients with lymphoma and fever; Eastern Cooperative Oncology Group (ECOG) performance status of 0–3 • Exclusion criteria: severe burns, severe trauma, recent major surgery, or autoimmune conditions and/or were unwilling to provide informed consent • *A priori* patient characteristics: ○ M/F: 55/25 ○ Median age: 60.5y ○ Cancer type: diffuse large B-cell lymphoma N=38, peripheral T-cell lymphoma N=12, Hodgkin's lymphoma N=6	Diagnostic test(s): Procalcitonin Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. no infection	CRITICAL OUTCOMES Optimal cut-off = 0.215 ng/ml • Sensitivity: 66.3% • Specificity: 61.5%	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification • Analysis on the level of febrile episodes
Yang 2019 EXCLUSION: only diagnostic accuracy data on distinction	• Design: retrospective cohort study • Funding: supported by the National Research Foundation of Korea (NRF) grant funded by	• Eligibility criteria: patients with hematological malignancies and a febrile episode • *A priori* patient characteristics: bacteremia vs. no bacteremia ○ M/F: 49/50 vs. 278/237	Diagnostic test(s): Procalcitonin and CRP Reference standard:	CRITICAL OUTCOMES • Sensitivity: • Specificity: • PPV: • NPV:	Level of evidence: … risk of bias • …

Study ID	Methods	Patient characteristics	Intervention	Results	Critical appraisal of study quality
between bacteremia and and no bacteremia	the Korea government (MSIP) (NRF-2017R1A2B4011181), Republic of Korea; CoI: EONE Laboratories provided support in the form of salaries for one author • Setting: single university centre, South Korea • Sample size: N=511 with 614 febrile episodes • Duration: unclear	○ Median age: 54 vs. 54y ○ Cancer type: AML N=215, ALL N=109, lymphoma N=114	Target disorder:	• AUC:	
Zhao 2018	• Design: retrospective cohort study • Funding: supported by the project of Science and Technology Hall of Hebei Province, China (15967708D); CoI: none • Setting: single university centre, China • Sample size: N=96 • Duration: unclear	• Eligibility criteria: patients with a diagnosis of NSCLC, axillary temperature >37.5°C, and the absence of neutropenia • *A priori* patient characteristics: ○ M/F: 65/31 ○ Median age: 66.5y ○ Cancer type: squamous cell N=51, adenocarcinoma N=42, large cell N=3	Diagnostic test(s): Procalcitonin and CRP within 2 days of onset of fever Reference standard: Clinical, radiological, and microbiological data Target disorder: Infection vs. no infection	CRITICAL OUTCOMES Tumour fever vs. localized bacterial infection • Procalcitonin: cut-off 0.55 ng/ml ○ Sensitivity: 73.5% ○ Specificity: 92.3% ○ PPV: 94.9% ○ NPV: 66.7% ○ AUC: 0.773 • CRP: ○ AUC: 0.545 Tumour fever vs. bloodstream infection • Procalcitonin: cut-off 0.44 ng/ml ○ Sensitivity: 76.2% ○ Specificity: 88.5% ○ PPV: 84.2% ○ NPV: 82.1% ○ AUC: 0.840 • CRP: ○ AUC: 0.786	Level of evidence: unclear risk of bias • Unclear selection process • Unclear blinding (probably none) • Reference standard not reported in detail; probably differential verification

Abbreviations: 95%CI: 95% confidence interval; AML: acute myeloid leukemia; AUC: area under the curve; CLL: chronic lymphatic leukemia; CoI: conflict of interest; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FUO: fever of unknown origin; HSCT: haematopoietic stem cell transplantation; ICU: intensive care unit; M/F: male/female; NHL: non Hodgkin lymphoma; NPV: negative predictive value; PPV: positive predictive value; US: United States.

References

Al Shuaibi, M., et al., Pro-adrenomedullin as a novel biomarker for predicting infections and response to antimicrobials in febrile patients with hematologic malignancies. Clinical Infectious Diseases, 2013. 56(7): p. 943-50.

Chang, J.C. and H.M. Gross, Utility of naproxen in the differential diagnosis of fever of undetermined origin in patients with cancer. American Journal of Medicine, 1984. 76(4): p. 597-603.

Chang, J.C., How to differentiate neoplastic fever from infectious fever in patients with cancer: usefulness of the naproxen test. Heart & Lung, 1987. 16(2): p. 122-7.

Debiane, L., et al., The utility of proadrenomedullin and procalcitonin in comparison to C-reactive protein as predictors of sepsis and bloodstream infections in critically ill patients with cancer. Critical Care Medicine, 2014. 42(12): p. 2500-7.

Diness, L.V., et al., Procalcitonin and C-reactive protein as markers of bacterial infection in patients with solid tumours. Danish Medical Journal, 2014. 61(12): p. A4984.

Ding, S., et al., Diagnostic Accuracy of Procalcitonin, Neutrophil-to-Lymphocyte Ratio, and C-Reactive Protein in Detection of Bacterial Infections and Prediction of Outcome in Nonneutropenic Febrile Patients with Lung Malignancy. Journal of Oncology, 2020. 2020.

Ebihara, Y., et al., Diagnostic performance of procalcitonin, presepsin, and C-reactive protein in patients with hematological malignancies. Journal of Clinical Laboratory Analysis, 2017. 31(6).

Hangai, S., Y. Nannya, and M. Kurokawa, Role of procalcitonin and C-reactive protein for discrimination between tumor fever and infection in patients with hematological diseases. Leukemia & Lymphoma, 2015. 56(4): p. 910-4.

Kallio, R., et al., C-reactive protein and erythrocyte sedimentation rate in differential diagnosis between infections and neoplastic fever in patients with solid tumours and lymphomas. Supportive Care in Cancer, 2001. 9(2): p. 124-8.

Kallio, R., et al., C-reactive protein, procalcitonin and interleukin-8 in the primary diagnosis of infections in cancer patients. European Journal of Cancer, 2000. 36(7): p. 889-94.

Mori, Y., et al., Diagnostic value of serum procalcitonin and C-reactive protein for infections after allogeneic hematopoietic stem cell transplantation versus nontransplant setting. Internal Medicine, 2011. 50(19): p. 2149-2155.

Penel, N., et al., Causes of fever and value of C-reactive protein and procalcitonin in differentiating infections from paraneoplastic fever. Supportive Care in Cancer, 2004. 12(8): p. 593-8.

Rao, L., et al., The ability of inflammatory markers to recognize infection in cancer patients with fever at admission. Immunologic Research, 2022. 70(5): p. 667-677.

Schuttrumpf, S., et al., Procalcitonin: a useful discriminator between febrile conditions of different origin in hemato-oncological patients? Annals of Hematology, 2003. 82(2): p. 98-103.

Shen, W. and S. Lai, Diagnostic Value of sCD163 Combined with PCT and HS-CRP in Patients with Gynecological Malignant Tumors and Fever. Jcpsp, Journal of the College of Physicians & Surgeons - Pakistan, 2020. 30(10): p. 1053-1057.

Vassallo, M., et al., Procalcitonin and C-Reactive Protein/Procalcitonin Ratio as Markers of Infection in Patients With Solid Tumors. Frontiers in Medicine, 2021. 8.

Vincenzi, B., et al., Procalcitonin as diagnostic marker of infection in solid tumors patients with fever. Scientific Reports, 2016. 6: p. 28090.

Wang, X.J., et al., Role of Procalcitonin in Differentiating between Infectious and Noninfectious Fevers among Patients with Lymphoma. Pharmacotherapy:The Journal of Human Pharmacology & Drug Therapy, 2017. 37(8): p. 908-915.

Zhao, Z., et al., Role of C-reactive protein and procalcitonin in discriminating between infectious fever and tumor fever in non-neutropenic lung cancer patients. Medicine, 2018. 97(33): p. e11930.