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ORIGINAL RESEARCH

Nonspecific complaints in emergency medicine: contribution of clinical chemistry and diagnostic imaging to final diagnosis. An observational study

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Abstract

Objective: To determine the contribution of history, physical examination, clinical chemistry, and diagnostic imaging to the validated final diagnosis in patients presenting with nonspecific complaints to the emergency department (ED).

Methods: This is a secondary analysis of Basel Non-specific Complaints (BANC), a multicentre prospective observational study. A final diagnosis was validated for every patient after a 30 days follow-up. A team of experts rated the contribution of the emergency work-up, and of clinical chemistry, diagnostic imaging, specialist consultation, and other exams to the final diagnosis.

Results: 612 non-trauma patients with NSC were prospectively included. After exclusion of 19 patients due to protocol violation or missing information, 593 patients were analysed. 412/593 (69%) validated final diagnoses were attributed to the ED work-up, and 181 (31%) to subsequent work-up by internal medicine, geriatrics, or outpatient clinics. Clinical chemistry was judged to be decisive for 300/593 (51%), and imaging for 106/593 (18%) of all final diagnoses. Chest radiography was decisive in 50 (8%), cranial computed tomography or magnetic resonance imaging in 21 (4%), and chest computed tomography in 10 (2%) cases.

Conclusion: Clinical chemistry and imaging contribute substantially to the diagnoses of patients presenting to the ED with NSC. However, post-ED-workup including consultations by specialists (e.g., neurology, geriatrics, psychiatry) were decisive for almost a third of all final diagnoses.

Keywords

Nonspecific complaints; Emergency medicine; Clinical chemistry; Diagnostic imaging; Physical examination

1. Introduction

Specific chief complaints usually provide key information allowing a working diagnosis, or may trigger predefined diagnostic protocols. Specific complaints are well-recognized as such in the literature, and diagnostic protocols are widely used in emergency medicine [1, 2]. In contrast to specific complaints, nonspecific complaints (NSC) can be defined as all complaints that are not part of the set of specific complaints or signs, or where an initial working diagnosis cannot be definitively established [3]. Typical NSC are generalized weakness, feeling exhausted, or falls of unknown origin [4]. Patients presenting with NSC have a higher risk of hospital admission, ICU-admission, prolonged hospital length of stay, and short- and long-term-mortality [5–7].

While history may contribute up to 70% to the definitive diagnosis in patients with specific complaints [8–11], it is virtually impossible to establish clear working diagnoses in patients with NSC by history taking and physical examination. Even though physical examination may add cues to working hypotheses, e.g., in pulmonary embolism [12], or endocarditis [13], its contribution to final diagnoses is often minimal in emergency medicine [14]. Thus, Sir William Osler's advice: "Let the patient, with history and physical examination, tell you the diagnosis…" [15] might no longer be valid, particularly in patients with NSC presenting to an ED. It was previously shown in another cohort that the proportion of correct diagnoses is low in emergency patients with nonspecific complaints [16]. We therefore attempted to determine the contribution of history, physical examination, clinical chemistry, and diagnostic imaging to the validated final diagnosis in patients presenting with nonspecific complaints according to the original definition by Nemec *et al.* [3]. We hypothesized that clinical chemistry and diagnostic imaging largely contribute to the validated final diagnosis.

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2. Methods

2.1 Study design

This secondary analysis of the BANC-study (Basel Non-specific Complaints), a multicentre prospective observational study, with a 30-day follow-up was conducted from 27 May 2009 through to 8 February 2011. The study was performed at the EDs of Basel University Hospital, Cantonal Hospital Liestal, and Cantonal Hospital Bruderholz, with an annual census of 20,000 to 50,000 patients. The study protocol was approved by the local ethics committee, all procedures were performed in accordance with the Helsinki Declaration, and all patients signed an informed consent form. The study protocol was approved by the local research ethics committee (EKBB 94/09) and the study is registered with ClinicalTrials.gov (NCT00920491).

2.2 Population and inclusion criteria

A validated German version of the Emergency Severity Index (ESI) was used to triage patients [17]. All adult (i.e., $\geq$18 years) non-trauma patients with an ESI of 2 or 3 (whose vital parameters were not markedly out of range, but were considered to be too sick for "see and treat") presenting to the ED with nonspecific complaints were eligible. According to the original BANC definition of NSC, only patients were included in which no working diagnosis was established after medical history and a first physical examination in the ED. Patients referred from other hospitals, patients referred with clinical chemistry results, or patients with vital parameters markedly out of range (systolic blood pressure $<$80 mmHg, heart rate $>$120 beats/minute, temperature $>$38.5 or $<$35.6 °C, respiratory rate $>$20 breaths/minute, SaO2 $<$92%), new electrocardiogram (ECG) abnormalities (new ST-elevation/left bundle branch block), patients who needed surgery, patients who did not sign the informed consent form, and patients with incomplete data were not included. Patients were prospectively enrolled Monday to Friday from 9 AM to 7 PM by a study team.

2.3 Data collection

Patient data were recorded in standardized case report forms filled out by study physicians at ED-presentation: Patient's demographic baseline data such as date of birth, ESI, vital signs, medical history, alcohol consumption, recent falls, decline of activities, medication, physical examination information, Glasgow Coma Scale (GCS), Charlson Comorbidity Index (CCI) [18], Katz Index of Independency in Activities of Daily Living [19] and cognitive testing (Clock drawing test) were collected. Double data entry was performed by two independent study nurses to transfer data from the case report forms to the study database (OpenClinica®).

Study variables: Diagnostic exams, such as clinical chemistry (sodium, potassium, chloride, calcium, phosphate, creatinine, urea, urate, glucose, ammonia, thrombocytes, leucocytes, haemoglobin, haematocrit, international normalized ratio (INR), mean corpuscular volume (MCV), ferritin, C-reactive protein, blood sedimentation rate, procalcitonin, blood-culture, albumin, transaminases, gamma-glutamyltransferase, alkaline phosphatase, bilirubin, troponin, creatinine kinase, brain natriuretic peptide (BNP), D-dimer, blood gas analysis, thyroid stimulating hormone (TSH), parathormone, vitamin D, vitamin B12, blood alcohol concentration, tox-screen, lithium level, valproate level, serum electrophoresis, syphilis serology, acetylcholine receptor antibodies, carbohydrate-antigen 19–9, carbohydrate-antigen 125, serum osmolality, urine osmolality, urine sodium, urine test strip, urinalysis, urine-bacteriology, urine-culture, pneumococcus-antigen, H2-breath test, influenza polymerase chain reaction), imaging (x-ray, computed tomography, magnetic resonance imaging, ultrasound-imaging, echocardiography, endoscopy, scintigraphy), electrocardiogram (ECG; formally categorized by study physicians into new ST-segment elevation, left bundle branch block, atrial fibrillation, and other abnormalities), consultations (neurologic assessment, geriatric assessment, psychiatric assessment), clinical follow-up, electro-encephalogram, and electroneurogram were performed at the discretion of the responsible physician. Data obtained from the hospital electronic database were electronically transferred to the study database.

Follow-up: For outpatients, 30-day follow-up data were obtained from the patient's primary care physicians using questionnaires. For hospitalized patients, hospital discharge reports and hospital electronic databases were used to obtain 30-day follow-up data.

Adjudication of final diagnoses: Final diagnosis was defined as the one diagnosis that was most closely related to the patient's initial presentation, and receiving the highest amount of attention (e.g., resources for treatment according to ICD-10 rules).

Final diagnoses were (1) made by at least two experts, board certified in internal and emergency medicine; (2) made 30 days after enrolment using all information available at this time point; (3) coded according to the ICD-10 rules; (4) grouped into clinically meaningful categories (infectious conditions, cardiovascular conditions, mental- and behavioural conditions, geriatric conditions, metabolic conditions, neurological conditions, neoplasms, renal failure, anaemia, gastrointestinal bleeding, and other).

Decisive Examination was defined as the exam containing the main piece of information provided for the final diagnosis. Typical examples are urinary or blood cultures for urinary tract infections, specific clinical chemistry for electrolyte disorders, or chest x-ray for pneumonia. For each patient, the responsible physician's notes, all clinical chemistry, all imaging results, all consultation reports, and all other reports, such as discharge letters and follow-up exams at outpatient clinics were available. In a first step, the final diagnosis was validated by experts on the basis of discharge and follow-up information. In a second step, all exams were presented to experts by a third physician, and all exams were rated as decisive or non-decisive for the validated final diagnosis. In a third step, experts compared the validated final diagnosis to the diagnosis made at the end of the ED work-up. If consensus was not achieved, two examinations could be called equally important for the final diagnosis.

2.4 Specific and non-specific complaints

Specific complaints were defined as, bleeding, fever, headache, chest pain, abdominal pain, dyspnoea, cough, vertigo, nausea, vomiting, diarrhoea, dysuria, swollen extremity, stroke-like symptoms, syncope, palpitations, skin lesion, allergic reaction, anxiety, psychotic symptoms, suicidal ideation, confusion, intoxication, or seizure.

Non-specific complaints were defined as all complaints that are not part of the set of specific complaints or signs, or where an initial working diagnosis cannot be definitively established. Most frequent NSC are weakness, not feeling well, fatigue, inability to walk, or unable to cope with usual daily activities.

2.5 Statistical analysis

Descriptive statistics are presented as counts and frequencies for categorical data, and median [interquartile range] for metric variables. All evaluations were done using the statistical software SPSS Statistics 27 (IBM Corporation New Orchard Road. Armonk, NY 10504).

3. Results

A total of 612 non-trauma patients with NSC were enrolled from May 26th 2009 until July 8th 2011. After exclusion of 19 patients due to protocol violation or missing information, 593 patients were included. Table 1 shows the baseline characteristics of the patients analysed. Median age was 82 years (IQR 75–87), and 359 (61%) were female. Follow-up was available for all patients.

In a total of 576 (97%) patients, clinical chemistry (electrolytes, kidney and liver function tests, CRP, and standard haematology), and in 447 (75%), urinalysis was performed. In 523 (88%), pro-calcitonin, and in 339 (57%), BNP was measured. An ECG was performed in 534 (90%), and a chest radiograph in 406 (68%).

The distribution of final diagnoses is shown in Table 2. A total of 412 (69%) validated final diagnoses corresponded to the diagnoses made after completion of ED work-up, and 181 (31%) validated final diagnoses corresponded to the diagnoses made at discharge from internal medicine or geriatric wards or outpatient clinics. Table 3 shows the contribution of different exams to the final diagnosis. Overall, clinical chemistry contributed to 300 (51%), and imaging to 106 (18%) of all validated final diagnoses. Chest radiography was decisive in 50 (8%), cranial computed tomography or magnetic resonance imaging in 21 (4%), and chest computed tomography in 10 (2%) patients. Secondary physical examinations led to the final diagnosis in one patient (0.2%), which turned out to be breast cancer, and none could be obtained from further history taking. For the most common diagnoses the distribution of decisive examinations was as follows: In UTI, clinical chemistry was decisive in 2 (2.8%) patients, urinalysis in 33 (45.8%), and urinalysis and clinical chemistry in 34 (47.2%). In pneumonia, clinical chemistry was decisive in 18 (42.8%), clinical chemistry and imaging in 15 (35.7%), and imaging in 7 (16.7%) patients. In heart failure, clinical chemistry was decisive in 32 (72.7%), clinical chemistry and imaging in 10 (22.7%), and ECG and clinical chemistry in 2 (4.5%) patients. In myocardial infarction, clinical chemistry was decisive in 9 (75%), clinical chemistry and imaging in 1 (8.3%), and ECG and clinical chemistry in 2 (16.7%) patients. In metabolic disorders, clinical chemistry was decisive in 56 (93.3%), and urinalysis and clinical chemistry in 2 (3.3%) patients. In neurological conditions, clinical chemistry was decisive in 10 (22.2%), clinical chemistry and imaging in 2 (4.4%), imaging in 13 (28.9%), and specialist consultation in 15 (33.3%) patients. In neoplasms, clinical chemistry was decisive in 5 (20.8%) patients, clinical chemistry and imaging in 3 (12.5%), imaging in 12 (50%), and clinical follow-up in 1 (3.3%) patient.

TABLE 1. Patients' characteristics.

Patients	n (%)
All	593 (100)
Male	234 (39)
Female	359 (61)
Age	median (IQR)
All	82 (75–87)
Male	79.5 (71–86)
Female	84 (78–88)
Living situation	n (%)
Home, independent,	233 (39)
Home, help from family/neighbours	62 (10)
Home, professional support	272 (46)
Nursing home	26 (4)
Mode of referral	n (%)
Self referral	68 (12)
Referral by family doctor	155 (28)
Referral by proxy	39 (7)
Referral by ambulance	289 (52)
Stay 30 days after presentation	n (%)
Tertiary care hospital	72 (12)
Geriatric hospital	267 (45)
Home	250 (42)
Morbidity	Median (IQR)
Charlson comorbidity index	5 (4–7)
Number of drugs	6 (3–9)
Katz index of daily activities	6 (5–6)

4. Discussion

The main results of this study are the high contribution of clinical chemistry and imaging to the final diagnoses in patients presenting to the ED with NSC. In detail, clinical chemistry was decisive in about half of all cases, and diagnostic imaging contributed to another 18%. Other exams, such as electrocardiogram or neurological consultation contributed in only 1% and 4% of the cases. While geriatric and psychiatric consultation performed post ED led to the diagnosis in 12% and 9% of the cases, only few diagnoses were made due to clinical

TABLE 2. Validated final diagnoses.

Diagnostic groups	Percentage	n
Infectious conditions	23%	137
Urinary tract infections	12%	72
Pneumonia	7%	42
Other infections	4%	23
Cardiovascular conditions	16%	99
Heart failure	7%	44
Myocardial infarction	2%	12
Pulmonary embolism	1%	5
Ischemic stroke	1%	6
Cerebral hemorrhage	1%	8
Orthostasis	1%	5
Other cardiovascular conditions	3%	19
Mental and behavioural conditions	13%	77
Anxiety, depression, somatisation disorder	8%	48
Substance abuse, intoxication	5%	29
Geriatric conditions	11%	69
Frailty	7%	43
Dementia	4%	26
Metabolic conditions	10%	60
Dehydration	3%	17
Electrolyte disorders	6%	35
Other metabolic conditions	1%	8
Neurological conditions	8%	45
Epilepsy	2%	10
Parkinsonism	2%	9
Polyneuropathy	2%	10
Other neurological conditions	2%	11
Neoplasms	4%	24
Renal failure	4%	24
Anaemia	2%	9
Gastrointestinal bleeding	1%	6
Other	8%	48

TABLE 3. Frequent decisive examinations for final diagnoses.

Decisive examinations at ED	n (%)
Clinical chemistry	266 (45)
Clinical chemistry and imaging	25 (4)
Imaging	71 (12)
ECG	7 (1)
Clinical chemistry and ECG	4 (1)
Consultation (Neurology)	23 (4)
Decisive examinations post ED	n (%)
Consultation (Geriatrics)	69 (12)
Consultation (Psychiatry)	56 (9)
Clinical follow-up	32 (5)
Imaging	7 (1.2)
Chemistry and imaging	4 (1)
Clinical chemistry	1 (0.2)
EEG or ENG	6 (1)

ED, emergency department; ECG, electrocardiogram; ENG, electroneurogram; EEG, electroencephalogram.

chemistry or imaging after completion of the ED-work-up.

To our knowledge, this is the first study showing that clinical chemistry and imaging, but not history-taking and physical examination are decisive in emergency patients presenting with NSC. However, to predict probabilities of diseases in other populations, there are a variety of models based on history and physical examination alone or in combination: The validated Canadian CT head rules are based mainly on history, and are 100% sensitive to exclude brain injury requiring surgical intervention in patients with minor brain injury [20]. Wells score and Geneva scores are validated tools to predict the pre-test probabilities of pulmonary embolism. They are mainly based on history and physical examination [12, 21]. All these clinical models are based on patients with specific complaints, which were not included in our study. Thus, such models are not applicable to patients with nonspecific complaints. In these patients, no evidence-based diagnostic work-up has been brought forward yet, making diagnostic decisions difficult. It is therefore important to know that about 30% of all final diagnoses were missed or delayed in this population, even in an environment where clinical chemistry and imaging is widely used. As the majority of our patients received laboratory examinations and imaging, it is not surprising that these modalities did not contribute much to the final diagnoses in patients with delayed diagnoses. After admission to geriatrics or internal medicine, specialist consultations, particularly by psychiatrists or geriatricians, were decisive for the majority of final diagnoses. These consultations may be difficult to organize in a four-hour throughput ED, and may not even be necessary in patients with subsequent admission. Therefore, ED diagnosis is largely based on clinical chemistry and imaging. However, limited sensitivities and specificities of laboratory tests must be considered during ED work-up —particularly regarding urinalysis and BNP: The sensitivity and specificity of leucocyte esterase in urine dipstick tests is reported to be 56% and 66%, and urine microscopy 56% and 72%, respectively, for a urine culture of 10^5 CFU/mL, in patients with urinary tract symptoms [22]. In an older population, it can be difficult to differentiate asymptomatic bacteriuria from urinary tract infection, and can lead to misdiagnosis of UTI [23, 24]. The criteria we followed to accept the diagnosis of UTI were the laboratory results (urinalysis and urine culture) and the 30 day observation. The experts decided on UTI only if a rapid clinical improvement of symptoms followed the antibiotic treatment. While the sensitivity of BNP may be 95% for heart failure, its specificity is much lower [25]. Although CRP and procalcitonin were added to the diagnostic criteria of sepsis [26], sensitivities and specificities regarding bacterial infection [27] and sepsis are low [28]. In

a meta-analysis including studies evaluating these markers in hospitalized patients, sensitivity and specificity of CRP was 80% and 61%, and of procalcitonin, it was 80% and 77%, respectively, for the diagnosis of sepsis [28]. Thus, when using clinical chemistry, operating characteristics should be considered at interpretation of these tests [29].

Our study had several limitations: first, the classification of nonspecific complaints implies a subjective judgment on the part of the EP. Such judgment depends on physician-related factors such as clinical experience and skills and on weighing the different complaints that may guide further assessment. Moreover, patient-related factors play a role and include the ability to verbalize complaints, the patient's cognitive status, or both. Second, the characteristics of ED physicians and physicians working on wards were not assessed. Thus, the influence of factors such as the physician's age and experience was not included in the analysis and the EP's interview and examination process have not been checked for fidelity. Third, patients were not enrolled consecutively, but only during business hours, and the number of potentially eligible patients that were not screened was not available. Thus, the magnitude of any selection bias could not be determined. Furthermore, environmental factors such as seasonality or overcrowding have not been recorded and could therefore not be included in this analysis.

In conclusion, laboratory tests and imaging contribute substantially to the diagnosis of patients presenting to the ED with NSC. However, a third of all diagnoses was made as a result of post-ED-workup, including consultations by specialists (e.g., neurology, geriatrics, psychiatrists).

AUTHOR CONTRIBUTIONS

AP, CHN, and RB designed the study, NRS and ASJ performed statistical analyses and drafted figures and tables, AP and RB drafted the manuscript, and AP, NRS, ASJ, CHN, and RB contributed to the final version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the local ethics committee, all procedures were performed in accordance with the Helsinki Declaration, and all patients signed an informed consent form. The study protocol was approved by the local research ethics committee (EKBB 94/09) and the study is registered with ClinicalTrials.gov (NCT00920491).

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Professor R. Bingisser had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The hypothesis of this study was made before the beginning of the collection of the data. The study protocol was written before the beginning of the collection of the data.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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