Stručni rad | Professional article

Trebamo li još uvijek pregledavati bolesnike?

Should we still examine our patients?

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SAŽETAK: Mnogi se liječnici danas nekritično oslanjaju na rezultate dijagnostičkih pretraga, što rezultira daljnjim nepotrebnim pretragama ili zahvatima. Ovaj rad prikazuje zašto to nije dobro i kakve su posljedice takve prakse.

SUMMARY: Many physicians today rely uncritically on the results of diagnostic tests, resulting in further needless examination and interventions. This article shows why this is incorrect and what the consequences of such practices are.

KLJUČNE RIJEČI: lažno pozitivan rezultat, pozitivna prediktivna vrijednost, kliničke vještine.

KEYWORDS: false positive results, positive predictive value, clinical skills.

CITATION: Cardiol Croat. 2017;12(1-2):3-5. | **DOI:** http://dx.doi.org/10.15836/ccar2017.3

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RECEIVED:
February 2, 2017

ACCEPTED:
February 20, 2017

Moderna je medicina, pa tako i kardiologija, obilježena brzim razvojem i primjenom novih dijagnostičkih metoda, i slikovnih i laboratorijskih. One s vremenom postaju sve osjetljivije i specifičnije te nam omogućuju ranije i pouzdanije otkrivanje i liječenje bolesti. Takav je razvoj događaja, međutim, u većine bolesnika (a, nažalost, i u većine liječnika) stvorio privid "objektivizacije" nečije bolesti, koji "nadilazi" puke znakove i simptome. Na primjer, u otkrivanju koronarne bolesti srca pregled zamjenjuje ergometrija, ergometriju zamjenjuje SPECT miokarda, SPECT zamjenjuje CT ili MR koronarografija; kardijalna dekompenzacija dijagnosticira se s pomoću RTG-a i NT-proBNP-a, a ehokardiografija postaje preduvjet za gotovo svaki invazivni zahvat ili operaciju. Pregled bolesnika i uzimanje anamneze na taj način polako postaju breme za liječnika, čiji je cilj što prije provesti određenu pretragu i doći do rezultata. Ti se pak rezultati također često interpretiraju tako da se pozornost posvećuje isključivo tomu je li neka vrijednost unutar ili izvan referentnog raspona. Svrha je ovog rada prikazati posljedice takvog postupka.

Svakom je kardiologu dobro poznata svakodnevna konzultacija s liječnicima drugih specijalizacija, a pogotovo s liječnicima hitne službe, zbog "troponinemije". Kolege zbog pravne nesigurnosti, a često i zbog neiskustva i neznanja u goto-

Modern medicine, including cardiology, is characterized by the rapid development and application of new imaging as well as laboratory diagnostic methods. These methods are becoming more sensitive and more specific, allowing us earlier and more reliable detection and treatment of diseases. Such development, however, has created the illusion of "objectification" of one's illness, which "goes beyond" mere signs and symptoms. For example, in the detection of coronary artery disease clinical examination is replaced by the exercise test, stress ECG is replaced by myocardial SPECT, SPECT is replaced by CT or MR coronary angiography, and so on; heart failure is diagnosed by X-ray and NT-proBNP, and echocardiography is becoming a prerequisite for almost any invasive procedure or surgery. The examination of patients and taking of medical history are slowly becoming a burden on physicians, whose goal is to implement a specific test as quickly as possible and get the results. These results, though, are often interpreted by paying attention solely to whether a value is within or outside the reference range. The aim of this paper is to show the consequences of such an approach.

Every cardiologist deals on a daily basis with calls from other physicians, especially in

vo svakom bolesniku vide akutni koronarni sindrom, a kao "zlatni standard" za postavljanje dijagnoze služi vrijednost troponina. Tako se troponin popeo na 15. mjesto najčešćih biokemijskih pretraga u hitnoj službi s relativnim udjelom od 40,77 % (Centar za hitnu medicinu KBC-a Zagreb, 2010. do 2014. godine; izvor: Golubić K.), sve zbog privida da su testovi nešto objektivno i apsolutno, na što mi nikako ne možemo utjecati, a liječnici kao ljudi neizbježno griješe. Tako dijagnostičke metode postaju spas u potrazi za načinom da se liječnika oslobodi razmišljanja ili mu pruže osjećaj da je nešto učinio.

Ono što se liječnik pita (ili bi se barem trebao pitati) kad interpretira rezultat nekoga dijagnostičkog testa jest: koja je vjerojatnost da moj bolesnik doista ima bolest pod uvjetom da je nalaz pozitivan? Osjetljivost i specifičnost nekog testa jesu relativno stalna obilježja nekog testa na koja baš i nemamo utjecaja, no ona nam ne odgovaraju na gore postavljeno pitanje (budući da mi ne znamo unaprijed tko je bolestan). Ono što liječniku treba jest pozitivna (ili negativna) prediktivna vrijednosti, a prediktivna vrijednost nekog testa ovisi o prevalenciji bolesti u skupini koja se testira.[1,2]

Neka nam za ilustraciju posluži ovaj primjer (**tablica 1**). Zamislimo da postoji uistinu dobar test koji otkriva bolest u 98 % bolesnih (osjetljivost) i vrlo dobro identificira ljude koji tu bolest nemaju (95 %-tna specifičnost). Koristit ćemo se istim testom u trima skupinama ljudi koje se razlikuju samo prema prevalenciji bolesti koju tražimo. U svakoj skupini neka bude 1000 ispitanika. Iako je primijenjen potpuno isti test, odgovor na pitanje u prvoj skupini (prevalencija 1 %) bio bi: samo 17 % pozitivnih ispitanika doista ima bolest, a u trećoj skupini (prevalencija 20 %) 83 % pozitivnih ispitanika doista ima bolest. Dakle, ako neka osoba iz prve skupine ima pozitivan test, veća je vjerojatnost da ona tu bolest nema nego da je doista ima, što je opet potpuno suprotno za ljude iz treće skupine.

TABLE 1. The dependence of the positive predictive value of a test on disease prevalence.

Prevalence (p)	1%	10%	20%
Diseased (d=px1000)	10	100	200
Healthy (h=(1-p)x1000)	990	900	800
True positives (TP=dx0.98)	10	98	196
False positives (FP=hx0.95)	50	45	40
All positives (AP=TP+FP)	60	143	236
Positive predictive value (TP/AP)	17%	69%	83%

Vrlo popularan pristup u novije vrijeme jest i istodobno izvođenje zajedno različitih testova (pogotovo tumorskih markera). Važno je istaknuti kako su referentne vrijednosti dobivene određivanjem srednje vrijednosti nekog testa u određenoj, najčešće zdravoj populaciji ± dvostruka ili trostruka standardna devijacija koje pokrivaju 95 % ili 99,7 % iste populacije. To znači da će uvijek postojati barem 5 % ili 0,3 % lažno pozitivnih bolesnika, ovisno o metodologiji kojom su dobivene referentne vrijednosti po jednome jedinom testu.

emergency services, because of "troponinemia". Due to legal uncertainty and often due to inexperience and ignorance, physicians see acute coronary syndrome in almost every patient and use troponin as a "gold standard" for establishing the diagnosis. Thus, troponin rose to the 15th the most frequently-ordered biochemical test in the emergency room with a relative share of 40.77% (Centre for Emergency Medicine, University Hospital Centre Zagreb, 2010-2014; Golubić K, unpublished data). All because of the illusion that tests are something objective and absolute, and something which we cannot impact, while doctors are only human and inevitably make mistakes. Diagnostic methods become a refuge in the search for a way to avoid thinking too much or give doctors a feeling that something was done.

What the physician asks themselves (or at least should ask) when interpreting the results of a diagnostic test is: what are the chances that my patient actually has the disease under the condition that the result is positive? The sensitivity and specificity of a test are relatively constant properties and we have no major influence on them, but they do not correspond to the above question (since we do not know who is truly sick). What the physician needs is a positive (or negative) predictive value of a test, and the predictive value of a test depends on the prevalence of the disease in the group being tested.[1-2]

Let use an example to illustrate this (**Table 1**). Imagine that there is a really good test that detects the disease in 98% of the sick (sensitivity) and identifies people who do not have the disease very well (95% specificity). We use the same test in three groups of people that differ only according to the prevalence of diseases that we seek. In each group there are 1000 people. Although we used exactly the same test, the answer to the question in the first group (prevalence 1%) would be: only 17% of positive respondents actually have the disease, and in the third group (prevalence 20%): 83% of positive respondents actually have the disease. So if a person in the first group has a positive test result, it is more likely that they do not have the disease, which again is completely opposite to people in the third group.

A very popular approach in recent times is executing a set of different tests (especially tumor markers) at the same time. It should be noted that the reference values for the tests are obtained by determining the mean value of a test in a specific, usually healthy population represent ± double or triple standard deviation covering 95% or 99.7% of the same population. This means that there will always be at least 5.0% or 0.3% false-positive results, depending on the methodology by which the reference values for the test are obtained. Let us look at what it means when multiple unrelated tests are performed simultaneously.

Take 10 simultaneous mutually independent biochemical tests whose reference values are obtained by taking the arithmetic mean value of a "healthy" population ± double standard deviation. The probability of getting at least one false positive value is:

according to $P(a)=1 - P(1) \times P(2) \times P(3)... \times P(n)$

$P(a)=1-(0.95)^{10}$

$P(a)=0.4$

Pogledajmo što to znači kad istodobno izvodimo više nepovezanih testova.

Uzmimo 10 istodobnih međusobno neovisnih biokemijskih testova čije su referentne vrijednosti dobivene uzimanjem aritmetičke sredine vrijednosti "zdrave" populacije ± dvostruka standardna devijacija. Vjerojatnost dobivanja barem jedne lažno pozitivne vrijednosti jest:

prema P(a) = 1 - P(1) x P(2) x P(3)... x P(n)

$P(a) = 1 - (0,95)^{10}$

P(a) = 0,4.

Dakle, vjerojatnost da potpuno zdrava osoba ima barem jedan "patološki" nalaz u ovome je slučaju 40 %, a ta se vjerojatnost povećava s rastućim brojem pretraga.

Još jedan omiljeni postupak liječnika jest da "provjere" kako bi bili "sigurni". Uzmimo primjerice da u hitnu službu dolazi 79-godišnji bolesnik te mu je nakon završene dijagnostičke obrade postavljena dijagnoza upale pluća, a, među ostalim, žali se i na bol u prsima. Iako nema ishemijskih promjena u EKG-u, liječnik odluči da će "za svaki slučaj" odrediti koncentraciju troponina. Test dolazi pozitivan (npr. troponin I = 67 ng/L), a liječnik zaključuje da bolesnik ima akutni infarkt miokarda bez elevacije ST segmenta (NSTEMI). Je li to točno?

Bol u prsima čest je simptom upale pluća te se pojavljuje u 79 – 91 % slučajeva[3]. Infarkt miokarda nepovezana je bolest te se u toj dobnoj skupini pojavljuje s učestalošću od 120/1000 godišnje[4], a upala pluća s učestalošću od 75/1000 godišnje[5]. Vjerojatnost (prije testiranja) da naš bolesnik ima i NSTEMI manja je od (120 x 75) / (1000 x 1000) = 0,009, dakle manja od 0,9%.[6] Imajući tu činjenicu na umu, potpuno je jasno da je vjerojatnost da bolesnik ima infarkt mnogo manja od vjerojatnosti da ga nema, čak uz povišeni troponin, kao što smo već vidjeli u prvome primjeru.

Iako su u ovom radu površno i pojednostavnjeno prikazani samo neki potencijalni problemi u predanalitičkoj (odabir ispitanika) i postanalitičkoj (interpretacija) fazi testiranja, jasno je vidljivo da je klinička korist od bilo kojeg testa jako ovisna o načinu na koji mi taj test ili pretragu upotrebljavamo. Najbolji način kako bismo smanjili krive interpretacije te izbjegli nepotrebno daljnje testiranje ili liječenje te eksponencijalno povećanje troškova liječenja bolesnika jest odabir ispitanika na temelju kliničkih vještina (povećavanjem prevalencije u ispitivanoj skupini) te izbjegavanja nepotrebnih dijagnostičkih metoda (bez kliničke sumnje u bolesnika s malom vjerojatnošću bolesti).

So the probability that a completely healthy person has at least one "pathological" finding in this case is 40%, and the likelihood increases with the growing number of tests.

Another popular approach is that the physician "checks" to be "sure". Take for example a 79-year-old patient with pneumonia diagnosed at the emergency department, complaining of chest pain. Although no ischemic changes were recorded in the ECG, the doctor decides to determine the concentration of troponin "just in case". The test is positive (eg. Troponin I = 67 ng/L), and the physician concludes that the patient has non-ST elevation myocardial infarction (NSTEMI). Is that correct?

Chest pain is a common symptom of pneumonia and occurs in 79-91% of the cases[3]. Myocardial infarction is an unrelated disease and, in this age group, occurs at a frequency of 120/1000 per year[4], while pneumonia occurs at a frequency of 75/1000 per year[5]. The pre-test probability that our patient has both pneumonia and NSTEMI is less than (120x75) / (1000x1000) = 0.009, i.e. less than 0.9%[6]. Keeping this fact in mind, it is clear that the probability that the patient has a myocardial infarction far lower than the probability that he does not have it, even with elevated troponin levels, as we have already seen in the first example.

Although this article only superficially and simplistically shows only some potential problems in the preanalytical (selection of respondents) and postanalytical (interpretation) phase of testing, it is clear that the clinical benefit of any test is heavily dependent on how we use it. The best way to minimize misinterpretation and avoid needless further testing or treatment and exponentially increase the cost of treating the patient, is with the selection of patients based on clinical skills (increasing prevalence in the study group) and avoiding unnecessary diagnostic methods (without clinical suspicion in patients with low probability of disease).

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