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Klinisk Biokemi i Norden

Nordisk Forening for Klinisk Kemi

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INDHOLD

Front page: *The winners of the NFKK Young Researcher Award (NYRA) and the organizers. From left: Lasse Back Steffensen (1st prize winner) from Denmark, Emil List Larsen (2nd prize winner) from Denmark, Selma Salonen (3rd prize winner) from Finland, Lars Melholt Rasmussen and Anders Larsson. Foto: Per Bjellerup.*

Leder:

Klinisk Biokemi og Diagnostikaindustrien: Harmoni og Konflikt

Linda Hilsted

Udviklingen i Klinisk Biokemi som medicinsk speciale er samtidig en historie om udviklingen i diagnostikaindustrien, og i dag kan Klinisk Biokemi ikke fungere uden et tæt samarbejde med industrien – og omvendt. Vi er afhængige af hinanden, og der er penge mellem os – mange penge. Det kræver selvfølgelig professionalisme på begge sider af bordet. Vi på hospitalerne har patienterne tæt inde på os i hverdagen, for diagnostikaproducenterne er de selvfølgelig længere væk, om end de altid fremhæves i firmaernes mission. Tillid er altid et stort ord, også i denne sammenhæng, men alligevel er mit udsagn, at generelt har vi som hospitalslaboratorier tillid til de leverandører, vi samarbejder med, for ellers ville vi jo stoppe samarbejdet. Eller?

Dette er en historie, om et samarbejde, hvor al tillid blev brudt. Det begyndte ellers så godt. En af de internationalt helt store og velrenommerede diagnostikaproducenter, som vi i vores afdeling har samarbejdet med gennem mange år, kom efter en længere udviklingsperiode på markedet med udstyr til medikamentanalyser på fuldblod, analyser hvor krav til analysekvalitet og svartider hidtil nærmest havde været uforenelige størrelser. Stor var glæden hos os, da vi efter udarbejdelsen af adskillige Business Cases, udbud og kontraktforhandlinger, ombygninger og installationer m.v. fik instrumentet i hus. Kontrakten var gældende i 7 år, med mulighed for 2 års forlængelse, og med betaling pr. test dvs. uden køb af udstyret. Samarbejdet med den lokale del af firmaet var forbilledligt, dygtige serviceteknikere i en vellykket installationsproces og træning af personale, og valideringen viste at analysekvaliteten var så god som lovet. Og ikke mindst at de lovede korte svartider kunne overholdes. Vores medarbejdere ved analyserne var fantastisk glade, for instrumentet var fuldautomatiseret, og presset for at nå at producere de livsvigtige svar blev meget mindre. Klinikerne var i den syvende himmel, for svarene kom meget tidligere på dagen end før. Alle var glade, i 11 måneder.

Så blev vi kontaktet af firmaet, der meddelte, at man med 5 måneders varsel ville tage instrumentet af markedet igen, ikke kun hos os, men også de andre steder, det var installeret i Europa. Ikke af kvalitetsmæssige årsager eller sikkerhedsmæssige årsager, men "for business reasons only". Anden forklaring fik vi ikke. Kontrakten, der på det tidspunkt havde en restperiode på lidt mere end 5 år, blev dermed brudt. Firmaet ville gerne foreslå en løsning i form af udstyr fra dem selv af samme type, som vi havde haft tidligere, dvs. ikke-automatiseret, og dermed = back to square one. Da der var tale om et klokkerent kontraktbrud, inddrog vi vores organisations advokater. Der fulgte mange møder med repræsentanter fra firmaet, og deres danske advokater, sammen med os og vores advokater. Vi var ikke interesserede i den instrumentløsning, firmaet foreslog – eller løsningens pris, bl.a. fordi tilliden nu kunne ligge et meget lille sted. Vi opgjorde og dokumenterede vores erstatningskrav, så minutiøst (=faktisk afholdte udgifter og et konservativt skøn over de afledte kommende udgifter) som det var os muligt. Men til vores store overraskelse blev vores udgifter bestridt af firmaet. Og forskellen var ikke beskeden. Mange yderligere møder fulgte, og parallelt med denne proces, var vi så nødt til at gå i "hasteudbud", få lavet kontrakt med et andet firma og indkøre udstyr af den gammeldags type. Udstyr, som vi jo vel og mærke skulle indkøbe, uden at have fået kompensation fra firmaet. Så efter måneders tovtrækkeri og forhandlinger blev der indgået et økonomisk forlig, der indebar et væsentligt økonomisk tab for vores afdeling. Vores advokater tilrådede dette forlig, selvom de var meget sikre på at en retssag ville falde ud til vores fordel, men det ville tidsperspektivet ikke.

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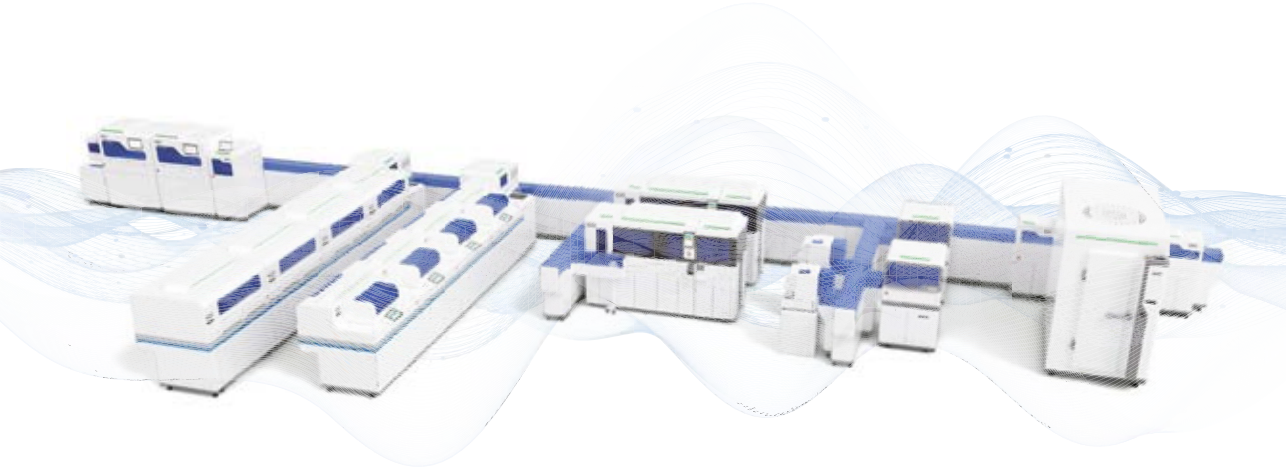

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Hvad var overraskende i hele dette forløb? Ja, selvfølgelig havde vi aldrig forestillet os, at et velrenommeret multinationalt firma ville bryde en kontrakt på denne måde. Men det, der nok overraskede mig personligt mest var, at selv i lyset af dette brud brugte firmaet mange resurser (inkl. advokatomkostninger) på at presse os ned i kompensation. Mens vi havde haft et fantastisk samarbejde med firmaets medarbejdere, var det tydeligt, at de ledere, der var sat på vores "sag", var af en helt anden støbning. Her handlede det tydeligvis kun om penge. Og det kan man undre sig meget over. Et kæmpe skår i firmaets troværdighed resterer.

Kan man gardere sig over for de andre industrielle samarbejdspartnere, vi har, så ingen i Klinisk Biokemi kommer ud i en lignende situation? En kontrakt, der bare brydes af sælger på den måde, har ingen af os vist oplevet før. Mit svar baseret på ovenstående må være nej, men hvem kan hjælpe os? Her peger pilen desværre på industrien, og det moralske kompas, industrien skal holde fast i – selv i sådanne ekstreme situationer.

Er der nogen læring i dette? Brød vi så samarbejdet efterfølgende med den resterende del af det multinationale firma? Nej – for der har vi en række afhængigheder på andre platforme og analyser og et godt samarbejde gennem en årrække.

Som regel har vi et fint samarbejde med de nationale firmarepræsentanter, der har en god forståelse for vores krav til analysekvalitet i Klinisk Biokemi i de danske/nordiske lande. For fx den danske del af et firma er det danske marked 100% og derfor meget vigtigt, men når større beslutninger skal tages, så flyttes beslutningerne meget længere væk, ofte over atlanten og hos økonomer og jurister. For dem er det danske (og nordiske) marked af meget lille betydning.

Risikoen er derfor altid, at de internationale firmaer ignorerer os i Norden og vores ønsker. Sådan er markedskræfterne. Tilsvarende gælder fx også for ustabile kalibreringer over tid. Vi klager, og vores nationale repræsentanter forstår os, men sagerne håndteres af firmaernes QC-sektioner som ikke er nationale, og som ofte afviser vores klager, med et svar hvor man fornemmer, at de synes vi er besværlige eller stiller urimelige(unødvendige) krav. Dialogen er nødt til at fortsætte, og her er det godt med et fortsat tæt og stærkt samarbejde de nordiske lande imellem og ikke mindst mellem landene og de nationale firmarepræsentanter.

Ordförandespalten

Per Bjellerup
NFKK chairman

Dear KBN reader!

The Congress!
From Helsinki in May 2018 to Stockholm in September 2024. It took six long years of waiting, and then, The XXXIX Nordic Congress in Clinical Chemistry did actually take place IRL during four hot and sunny days at Karolinska Institutet-Karolinska University Hospital.

I believe the Congress was a great success, and I would like to thank all the contributors for all good work conducted under the eminent leadership of **Charlotte Gran** at Karolinska University Laboratory!

My gratitude also goes to everyone who participated, as attendees, exhibitors, speakers or sponsors, without you - no Congress. ***Thank you all!***

The NFKK Young Researcher Award (NYRA)
I am particularly pleased that we could upheld the tradition of honouring and promoting emerging researchers in our field through the NFKK Young Researcher Award (NYRA). This award succeeds the Astrup Prize, established in 1979 by Radiometer A/S to honour Professor Poul Astrup for his pioneering work in medical acid/base chemistry and blood gas research. From 2010 to 2018, Siemens Healthineers generously sponsored the award. Moving forward, all expenses associated with NYRA will be incorporated in the Congress budget.

Of the nine applications, three of them were selected for presentation at the Congress and for the final division of the funds. You can read about the work by Emil List Larsen and Selma Salonen in this issue. In the next issue you will find the presentation by Lasse Bach Steffensen.

Grand start of the Congress
The Congress opened with an engaging presentation by Professor Borge Nordestgaard from Copenhagen on *Lipid profile and cardiovascular disease*. A most interesting and clear-cut lecture bringing order in this very complex field. Professor Nordestgaard has done a tremendous work, e.g. been mentor for 71 successful PhD students.

Grand finish of the Congress – with a glimpse of the future
The very last session about *Clinical metabolomics, a new era for laboratory medicine* was an eyeopener for what *Clinical Chemistry* will look like in the not so far future. Professor Ron Heeren from Maastricht described the new physical technology developments in mass spectrometry based chemical microscopes! We will be able to capture disease complexity to chart and connect multilevel molecular information within a tissue using mass spectrometry based molecular microscopy. To be successful in his work, Professor Heeren also has used the latest technique in the Cern laboratories.

This, dear colleagues, represents the promising future of our laboratories!

Meanwhile, enjoy the last days of autumn, soon the snow will be upon us!

Sincerely yours, Per

Aula Medica. Photo: Per Bjellerup.

Summary and Thanks – 39th Nordic Congress of Clinical Chemistry

Charlotte Gran
on behalf of the organizing committee
charlotte.gran@regionstockholm.se

The 39th Nordic Congress of Clinical Chemistry has now concluded, and we are proud to have hosted such a vibrant gathering of renowned experts and dedicated participants from around the world. With over 450 attendees from 20 countries, spanning from the USA to Australia– and the majority of participants from the Nordic countries – the congress served as a dynamic hub for science and innovation. More than 100 speakers shared their insights on topics ranging from the history of clinical chemistry to cutting-edge research. A longside scientific presentations, the congress offered educational sessions and inspiring discussions around quality and control within laboratory operations.

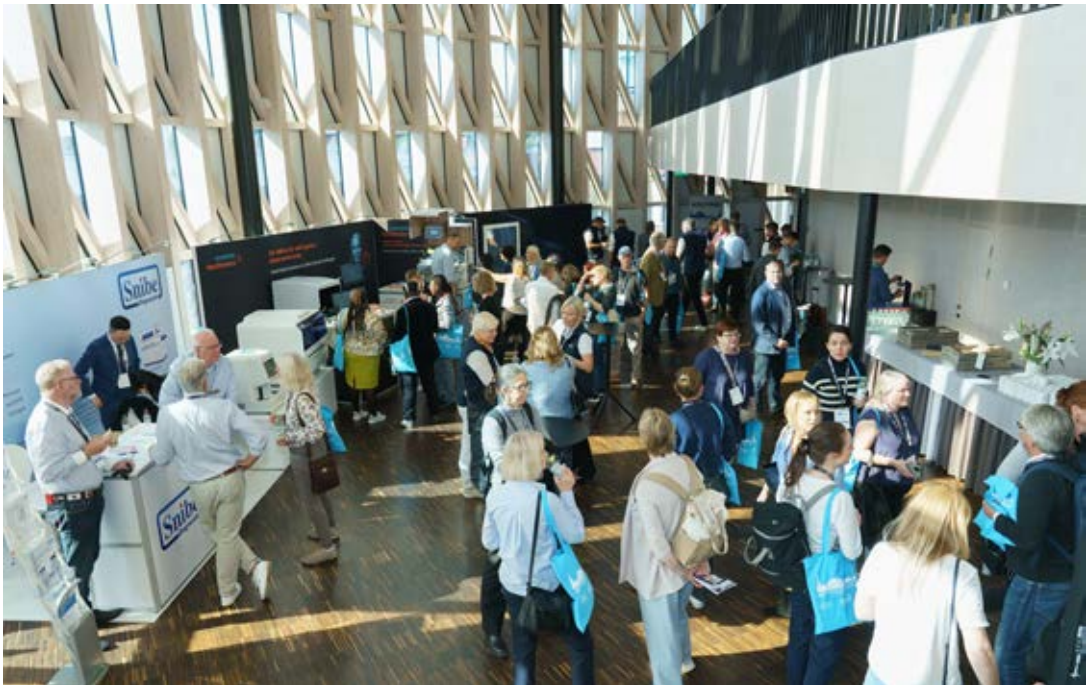
We are deeply grateful to all the speakers who shared their expertise, both in the lecture halls and in spontaneous conversations during the breaks. We were also pleased to meet with 70 company representatives from 27 different companies who sponsored the congress and contributed to its success. A special thanks goes out to all researchers who contributed with oral presentations and posters. Several prestigious awards were given out during the congress, including the Lorentz Eldjarn Prize and the new NFKK Young Researcher Award, with highly competitive presentations that enriched the atmosphere with inspiration.

During the congress dinner, held at the Vasa Museum and beginning with an exciting, guided tour, we announced the winners of the poster prizes in the Improvement and Development and Scientific categories. In the Improvement and Development track, the first prize was awarded to Iida Silvo from Labquality in Finland for her poster, "External quality assessment reveals lack of harmonization in the pneumatic tube systems and hemolysis index cutoffs," while the second prize went to Anne Jämse from Karolinska University Hospital in Sweden for her work on "Reduced interference in protein electrophoresis after storage of serum samples in room temperature." Within the Scientific track, the first prize went to Tapio Lahtiharju from Helsinki University Hospital in Finland, with his poster titled "Ferritin outperforms other biomarkers in predicting bone marrow iron stores in haematological patients," and second prize was awarded to Johannes Østrem Fjøse from Fürst in Norway for "Age-adjusted reference intervals for PSA in Norway based on the Norwegian Prostate Cancer Consortium (NPCC)."

We would also like to extend a heartfelt thanks to the colleagues from all units and sections within ME Clinical Chemistry at MDK. Through their efforts in various workgroups in preparation for the congress and as volunteers during the event, they provided invaluable support to speakers, participants, and sponsors every day. Their dedication and on-site assistance were instrumental in creating a welcoming and seamless congress experience for everyone involved.

We already look forward to the next congress in Århus 2026, and to continued advancements in clinical chemistry and laboratory medicine!

The congress was officially opened by the organizing committee in the plenary hall in Aula Medica. Photo: Per Bjellerup



The sponsor exhibition, located in Aula Medica where the plenary sessions took place, provided countless opportunities for engaging micro-meetings and networking among participants. Photo: Luxlucid/www.greenpix.se

En gjenforening preget av god kjemi: den nordiske kongressen er tilbake

Ingrid Hokstad
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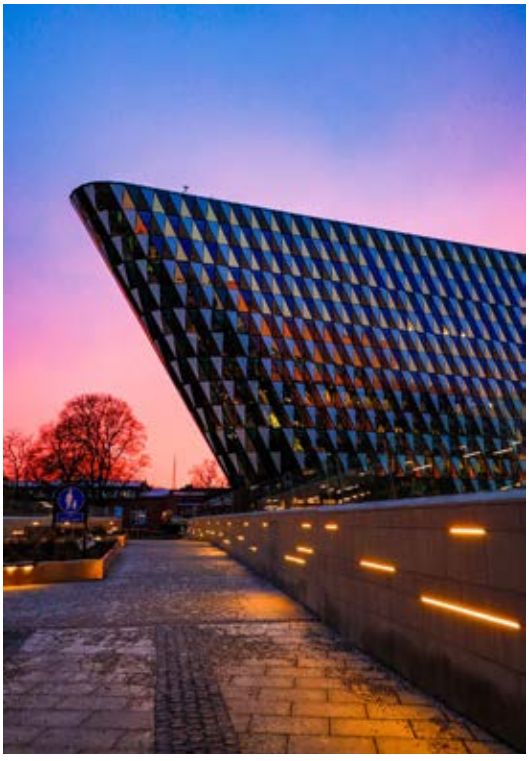
Etter flere år med avlyste nordiske kongresser grunnet koronarestriksjoner var det endelig duket for en ny samling; den 39. nordiske kongressen i laboratoriemedisin. Arrangørbyen Stockholm viste seg fra sin beste side; etter en bedrøvelig sommer preget av regn og dunjakkevær var det deilig å spasere lettkledd rundt under skyfri himmel hos "søta bror".

Kongressen fant sted ved Karolinska Institutet (KI), hvor det spektakulære bygget Aula Medica bokstavelig talt glitret med sin fasade prydet av 6000 triangulære glassplater. Det gir unektelig en ekstra piff til forelesningene å vite at man sitter i en sal hvor det holdes nobelforelesninger! Mens KI ble grunnlagt i 1810 av kong Karl XIII. for å utdanne feltskjærer, var det lite som vitnet om krigskirurgi når man entret Karolinska Universitetssykehuset i dag: De moderne omgivelsene fremstår som et kongressenter eller hotell, og man aner knapt at man befinner seg på et sykehus før man ser skiltene om blodprøvetaking.



Kongresskomiteen hadde satt sammen et bredt program med stor variasjon i faglige temaer. Det var stort fokus på nye teknologier og metoder, med en god balanse mellom grunnforskning og klinisk anvendelse. Det var dessuten en fin miks av faglige presentasjoner, prisutdelinger, diskusjoner og undervisningssesjoner. Et perspektiv man kanskje kunne savne, var etiske og praktiske avveininger knyttet til all den nye teknologien: Hvordan vil dens anvendelse påvirke viktige endepunkter som pasientens overlevelse og livskvalitet? Hvordan vil integreringen av slik teknologi påvirke arbeidsflyt og kostnader? Og hva blir vår rolle som laboratorieleger oppe i det hele? Dette er spørsmål vi bare kan spekulere rundt, men slike refleksjoner bør ligge i bakhodet på oss alle når forførende nye metoder og teknologier inntar laboratoriene våre.

"Development and improvements" var en ny temabolk som kompletterte resten av det vitenskapelige programmet på årets kongress. Presentasjonene her omhandlet utvikling og forbedring innen laboratoriemedisin, tverrfaglig samarbeid, og emner som kunstig intelligens, mangfold, inkludering, og bærekraft. I tillegg inneholdt programmet egne utdanningssesjoner hvor både mer og mindre erfarne morgenfugler kunne få med seg en innføring i spesifikke tema før hovedprogrammet startet for dagen. For norske leger i spesialisering, var det spesielt gledelig at Norsk Forening for Medisinsk Biokjemi dette året valgte å

sponse deres deltagelse på kongressen, noe som resulterte i god oppslutning også blant ikke-spesialister.

Fest og sosialisering var selvfølgelig også på programmet: Mingling og underholdning under åpningsseremonien, middager og mer eller mindre uformelle treff og middager. Torsdag kveld var det festmiddag og guidet omvisning i Vasamuseet. For oss som jobber med kvalitetssikring var Vasaskipets skjebne en rystende påminnelse om hvor galt det kan gå når man ikke opererer etter visse ISO-standarder. Å sitte ved siden av det enorme skipsvraket ga uansett en ekstra dimensjon til en flott middag, der våre svenske kolleger og arrangører av kongressen fikk velfortjent skryt for gjennomføring og planlegging.

Å kunne møtes online er praktisk, og nedstengninger i koronaperioden fungerte som et nyttig "spark i baken" for å fremskynde bruk av digitale kommunikasjonsverktøy. Men begrepet "zoom-fatigue" eksisterer av en grunn; selv om alle disse digitale møtene har hjulpet oss, har de også fremhevet verdien av å treffes ansikt-til-ansikt. Selve innholdet i en PowerPoint-presentasjon utgjør bare en brøkdel av utbyttet fra slike arrangementer: Vel så viktig er samtalene, ideene, fellesskapsfølelsen, og det å bli bedre kjent med kolleger man ikke omgås til vanlig. For oss som jobber på mindre sykehus er det uvurderlig å knytte kontakt med likesinnede på tvers av foretak, og de fleste lableger viser seg å være usedvanlig hyggelige folk!

Stor applaus til arrangørene av kongressen: Charlotte Gran fikk velfortjent pris eller skryt for å ha ledet prosessen på en eksemplarisk måte. Takk også til alle dyktige foredragsholdere, og ikke minst til kolleger som holdt fortet på laboratoriet hjemme mens vi andre var bortreist.

For oss småbarnsforeldre var det befriende å bare eksistere en uke uten å måtte rydde legoklosser, koke havregrøt og henge opp klesvask. Jeg reiser hjem med inspirasjon og motivasjon til å fortsette arbeidet, og med en skriveblokk full av faglige tema og ideer å sjekke ut.

Neste nordiske kongress finner sted i Århus 2026 og jeg gleder meg allerede til å se hva danskene har å by på!

Guided tours of the historic Vasa ship kicked off the congress dinner, offering participants a memorable experience. Photo: Helle B. Hager.

Kongressen - Nordisk Forening for Klinisk Kemi (NFKK) – *med naive briller*

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Som ny læge i faget klinisk biokemi fik jeg muligheden for at tage til NFKK kongressen i Stockholm, for at præsentere forskningsdata. Da jeg længe har været underlagt online-møder og restriktioner på rejse-aktiviteter grundet enten Corona-virussen eller omstændigheder i arbejdslivet, glædede jeg mig til endelig at komme ud over Danmarks grænser igen, og blive stimuleret af nye indtryk og viden. Jeg glædede mig tilsvarende til også endelig at hilse på mine kolleger i faget, da klinisk biokemi jo ikke er verdens største speciale (i al fald på lægesiden).

Stockholm var en flot, ren og pulserende by, og heldigvis rimeligt nem at finde rundt i. Vejret bød på 20 grader, blå himmel og høj sol. Det hjalp også gevaldigt, at Stockholms-svenskerne faktisk slet ikke virkede til at have megalomane følelser om at være "Skandinaviens storebror", men derimod var helt nede på jorden. Nogen vil måske endda gå så langt som til at sige, at de mindede gevaldigt om os danskere (chokerende ikke?!).

Hotellet (Elite Palace Hotel) og det hotelværelse jeg blev indlogeret på, var tilsvarende en meget positiv oplevelse. Ingen børnebrok over altid at få havregryn til morgenmad og ingen nonchalant henkastede underbukser der rodede på gulvet, men derimod meget indbydende, rent og ryddeligt. Selve kongressen fandt sted i Aula Medica (hørende til Karolinska Instituttet) ca. 20 minutters gåtur fra hotellet. Bygningen var flot og futuristisk, og indenfor sad en masse ivrige sjæle klar til at forklare mig praktikaliteterne omkring kongressen og vigtigst af alt: Hvor jeg skulle hænge min "ukrøllelige" (det var i hvert fald hvad trykkeriet havde sagt) medbragte poster op henne, som nu desværre efter en rum tid i håndbagagen, alligevel var blevet ret krøllet. Men hul i det, jeg følte mig velkommen!

Efter en lille åbningsceremoni gik kongressen og de planlagte foredrag officielt i gang. Foredragene var generelt rigtigt spændende og velpræsenterede, og det fungerede godt med, at der kørte 3 spor af forelæsninger, så man næsten altid kunne finde noget, der fik ens blod lidt i kog. Spændet i de præsenterede emner var enormt, med alt lige fra systemer til transport af blodprøver, åreforkalkning som en potentiel neoplastisk proces, LDL, VLDL-kolesterol, og Lp(a) som roden til alt ondt, samt vingeskydning af HDL som frelseren, biomarkører for demens, global metabolomics, og sci-fi-lignende apparater der i teorien skulle kunne kigge på human væv helt ned på atomart niveau. Det var også rigtigt fedt at se nogle af fyrtårnene inden for vores felt, som jeg nu endelig kan sætte ansigter på.

Selvom jeg var godt tilfreds med det faglige indhold, ville jeg dog have ønsket, at der havde været et større fokus på at facilitere det sociale aspekt af kongressen. Udover den planlagte poster-session var der ikke lagt udtalt meget op til, at man kunne diffundere rundt og "mingle". Som novice i faget vandrede jeg til tider lidt hvileløst rundt - og det er på trods af, at jeg normalt ikke har problemer med at etablere menneskelig kontakt. Sat lidt på spidsen, så fik jeg i virkeligheden nok snakket mere med firmaet der havde lavet en automatisk blodprøvetagningsrobot end mine yngre lægelige kolleger. Jeg savnede mest af alt blot nogle små events hvor f.eks. reservelæger fra de forskellige lande helt naturligt kunne mødes omkring en kop kaffe, eller en lille workshop hvor man kunne lære hinanden lidt bedre at kende. Som læger er vi jo allerede en minoritet i faget, så det ville have været alletiders med lidt hjælp til at finde hinanden. Bevares, jeg havde da nogle rigtigt hyggelige øjeblikke (en neon-belyst noget alternativ restaurant f.eks.) med de to speciallæger, der var med fra vores afdeling, men jeg nåede blot aldrig rigtigt at finde ud af hvem mine yngre læge kolleger fra Skandinavien egentlig var.

Men når det er sagt, så føler jeg heldigvis stadig efter hjemkomsten fra Stockholm, at jeg har fået en positiv en på opleveren! ..og ville jeg tage med til NFKK næste gang? – bestemt!

Første uddeling af NFKK Young Researcher Award (NYRA)

Lars Melholt Rasmussen[1], Per Bjellerup[2]
[1]Award committee chairman
[2]NFKK chairman

Ved den 39. nordiske kongres i klinisk biokemi afholdt i september i Stockholm blev NFKK's nye videnskabelige pris, NYRA (NFKK Young Researcher Award), uddelt for første gang. Prisen erstatter den tidligere Astrup-pris, som var sponsoreret af Siemens Healthineers, og er nu NFKK's egen pris, finansieret i forbindelse med de nordiske kongresser i klinisk biokemi.

For faget klinisk biokemi er det afgørende at tiltrække og støtte dygtige medarbejdere med høj videnskabelig kompetence. Klinisk biokemi er et videnstungt speciale, hvor forståelse og erfaring med en bred vifte af videnskabelige områder er helt centrale. Faget udvikler sig konstant, og derfor er en dyb forståelse af biokemiske og molekylære mekanismer, avancerede kemiske teknologier, datahåndtering (herunder kunstig intelligens) samt kliniske aspekter essentielt for at drive udviklingen fremad. Det er derfor naturligt for NFKK at støtte denne udvikling ved at tildele priser til yngre forskere, som fremmer deres kompetencer gennem videnskabeligt arbejde.

Ved årets kongres i Stockholm var indkommet 9 abstrakts og evalueringskomitéen udvalgte de tre bedste til konkurrencen om første, anden og tredje prisen. Efter de tre præsentationer på kongressens sidste dag blev det afgjort at Lasse Bach Steffensen fra Odense, Danmark vandt første prisen på 40.000 DKr på baggrund af et abstrakt om somatiske mutationer i åreforkalkningsplaque. Emil List Larsen fik anden prisen (20.000 DKr) for en præsentation om heparin-induceret trombocytopeni og Selma Salonen tredje prisen (10.000 DKr) for et abstrakt om måling af lange typer af troponin T. Det videnskabelige niveau blandt de tre detaljere var meget højt og der var udbredt enighed om, at alle tre yngre forskere var utrolige dygtige til at præsentere deres videnskabelige resultater.

Vi ser nu frem til om cirka et års tid at kunne annoncere en ny omgang med NYRA, som vil blive afholdt ved næste nordiske kongres i Århus i 2026. Det glæder vi os til.

De tre prisvindere, fra venstre: Emil List Larsen (anden pris), Selma Salonen (tredje pris) og Lasse Bach Steffensen (første pris). Foto: Per Bjellerup.

NYRA 2nd prize:

Accuracy of Diagnosing Heparin-induced Thrombocytopenia

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Heparin is a glycosaminoglycan that has a unique pentasaccharide sequence with anticoagulant properties. The drug has been used for almost a century for different indications. Heparin can be used prophylactically, therapeutically against venous and arterial thromboses, and as catheter patency. Thus, many patients receive heparin; especially during a hospital stay. The frequent usage is also due to the general safe profile, where bleeding and skin lesions are most common side effects. A rare but severe complication is, however, immune-mediated heparin-induced thrombocytopenia (HIT) (1).

A rare and severe complication

HIT is a rare complication that is most common following treatment with unfractionated heparin (<1-3%) compared with low-molecular-weight heparin (<0.2%) (2). Unfractionated heparin is a larger molecule and negatively charged; thus, it has a more unpredictive pharmacodynamic profile. The thrombocyte count must, therefore, be monitored when treating patients with unfractionated heparin. Even though the complication is rare, it is a severe one. The thrombosis incidence is estimated to 30-50% and the mortality rate is reported to be 9-30% when a HIT diagnosis is present (2).

Pathophysiology

When platelets are activated, they change conformation and release the contents of their intracellular granules. The granules contain different proteins, including platelet factor 4 (PF4). PF4 is a positively charged protein that binds to negatively charged surfaces, e.g.,

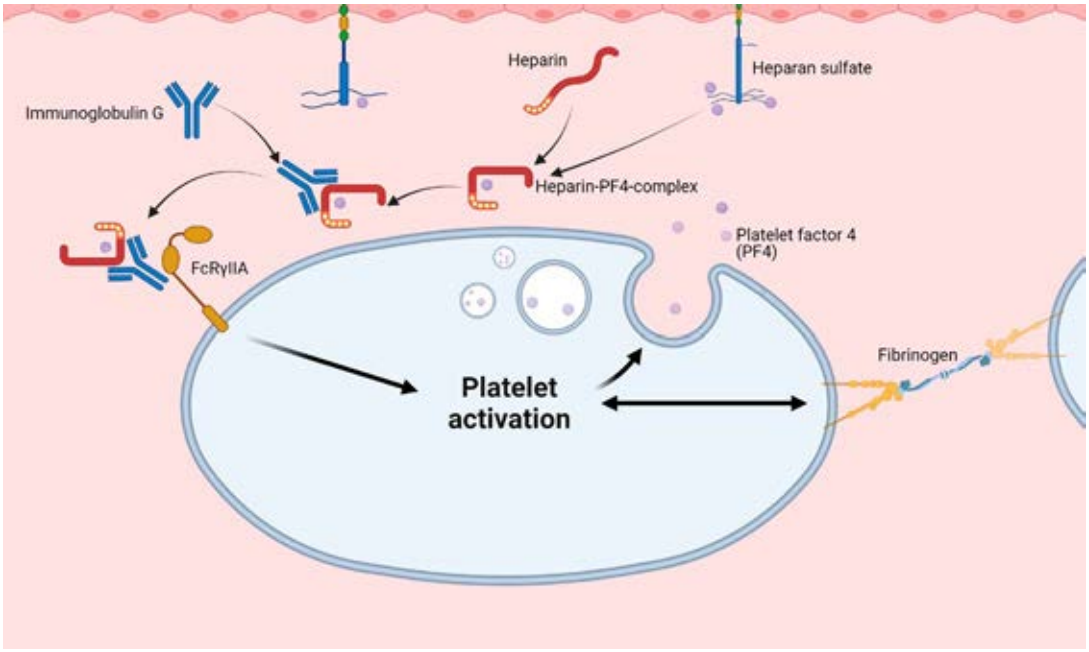

Figure 1. *Granules containing platelet factor 4 (PF4) are released when the platelets are activated. PF4 is a positively charged protein that binds to negatively charged surfaces, e.g., heparan sulphate. When heparin is administered, it has a higher affinity for PF4, and thus, PF4 is displaced from heparan sulfate into the circulation in complex with heparin. Sometimes, the immune system generates antibodies targeted at heparin-PF4-complexes. Hence, large immune complexes may be generated. If the immune complexes activate platelets through FcRγIIA, heparin-induced thrombocytopenia occurs. The figure has been modified and reused from DSTH Forum 2023, 3rd edition, with permission from copyright holders (11). The figure has been created in Biorender.com.*

heparan sulphate on the vessel surface, when released into circulation. Heparin has a higher affinity for PF4 than heparan sulphate. Thus, when administering heparin, PF4 will displace from the vessel surface into circulation in complex with heparin. Sometimes, the immune system generates antibodies targeting the heparin-PF4-complexes, and large immune complexes may be generated which – in certain cases – are able to activate platelets through FcRIIa **(Figure 1)**. If so, HIT may develop (3). The clinical presentation includes moderate thrombocytopenia that will rarely cause bleeding symptoms. Instead, thrombosis may occur because of the aggregation of thrombocytes (4).

The timing of thrombocytopenia depends on the antibody formation. If the patient has been treated with heparin before, however, thrombocytopenia may occur immediately following heparin administration. If the patient has not received heparin before, the naïve b-cells need to be activated and generate plasma cells that secrete antibodies. Therefore, the classical timing of thrombocytopenia is 5-10 days in patients who have not received heparin before. These three clinical hallmarks: *Thrombocytopenia*, *thrombosis,* and the *timing of thrombocytopenia* combined with *other causes of thrombocytopenia* are used to calculate a clinical risk score: the *4Ts score* (4). If the clinical risk score is elevated, laboratory testing of heparin-PF4-complex antibodies should be determined. Heparin-PF4-complex antibodies do not per se cause HIT. Therefore, in the presence of heparin-PF4-complex antibodies, a functional test should be performed to evaluate whether the antibodies activate platelets. If the heparin-PF4-antibodies activate donor platelets, this is compatible with HIT (5).

The diagnostic algorithm, serial combining the 4Ts score and heparin-PF4-complex antibody assay, is recommended by the American Society of Hematology (5). Even though a meta-analysis showed a high negative predictive value of the 4Ts score (6), a more recent study questioned the sensitivity of the 4Ts score

(7). Likewise, the sensitivity of rapid immunoassay for detection of heparin-PF4-antibodies varies among assays (8). Thus, we aimed to access the accuracy of the recommended diagnostic algorithm for suspicion of HIT.

1318 patients with suspected HIT

In the awarded study (9), a total number of 1318 patients suspected of HIT were included from eleven study centers. Defined by the functional test (heparin-induced platelet activation (HIPA) test), 111 (8.4%) had definitory HIT. Of the 111 patients with HIT, 98 (88.3%) had received unfractionated heparin within 2 weeks, and 52 (46.8%) had thrombosis when included. The patients with HIT were primarily included from intensive care units (n=38 (34.2%)) or were postoperative following cardiovascular surgery (n=46 (41.4%)) (9). In the study, we found that – using the 4Ts score – 592 (49.0%) were false positives and 10 (9.0%) were false negatives. Using a heparin-PF4-complex antibody chemiluminescence immunoassay, 73 (6.0%) were false positives and 5 (4.5%) were false negatives. Using the recommended diagnostic algorithm, i.e., serial combining the 4Ts score and chemiluminescence immunoassay, 50 (4.1%) were false positives and 15 (13.5%) were false negatives. As such, the recommended diagnostic algorithm had a sensitivity of 86.5% (95% confidence interval: 78.7; 92.2%) and a specificity of 95.9% (95% confidence interval: 94.6; 96.9%) (9).

Conclusions and perspectives

In conclusion, the recommended diagnostic algorithm for suspicion of HIT diminishes the need for laboratory testing. However, a concerning number of patients were still misdiagnosed (9). New algorithms have been proposed that combine clinical findings with results from heparin-PF4-complex antibody tests to improve the diagnostic accuracy. Here, the concentration of the antibody test is used instead of a binary endpoint (i.e., "negative" vs. "positive") (10). Furthermore, the 4Ts score was designed when unfractionated heparin was used more frequently and thus not integrated in the clinical risk score (i.e., 4Ts score). It has been suggested to integrate the information of heparin usage in a newer diagnostic model (10). Given the availability of heparin-PF4 complex antibody testing in many laboratories, it may be time to modify the recommended diagnostic algorithm in patients suspected of heparin-induced thrombocytopenia.

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NYRA 3rd prize:

Highly sensitive immunoassay for long cardiac troponin T

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Cardiac troponins (cTn) are the biomarkers of choice for the diagnosis of acute myocardial infarction (AMI) (1). However, commercial high-sensitivity cTn (hs-cTn) assays detect cTn elevations also in various other cardiac and non-cardiac conditions such as heart failure, atrial fibrillation, chronic kidney disease and strenuous exercise (2). This may often complicate the interpretation of the test results and thus, there is a clinical need for an assay which could better discriminate AMI from other conditions associated with hs-cTn elevations.

Fragmentation of cardiac troponin T in AMI and other conditions

Cardiac troponin T (cTnT) is prone to proteolytic degradation. A combination of intact cTnT molecule (approximately 40 kDa) and cTnT fragments of different sizes (8–37 kDa) is found in the blood of AMI patients (3–6). The commercial hs-cTnT assays that are currently used in hospitals target the stable central region of cTnT and recognize intact cTnT as well as degraded forms of cTnT (i.e. total cTnT) (3). However, intact and mildly degraded forms of cTnT (i.e. long cTnT forms) have been recently proposed to be a promising and more specific biomarker of AMI, as they have been predominantly found in early-presenting AMI patients. Small cTnT fragments seem to be the prevailing forms later after AMI, in marathon runners and in patients with end-stage renal disease (ESRD) (3–8).

Improved sensitivity with upconversion luminescence technology

Recently, a promising time-resolved fluorescence (TRF) immunoassay was developed for the detection of long cTnT forms showing improved specificity for

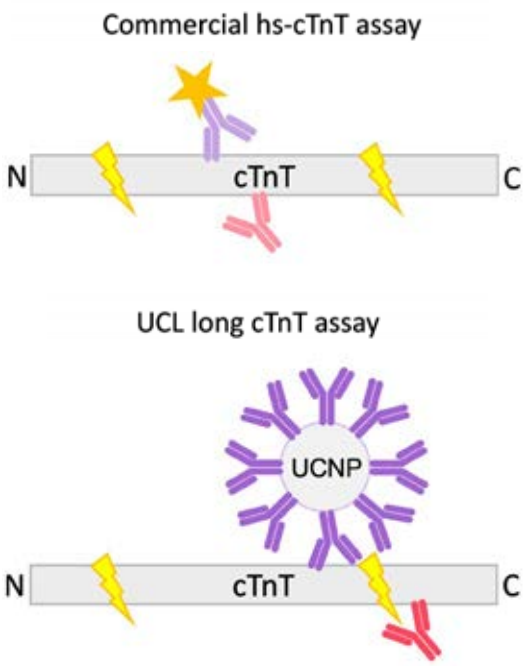

Figure 1. *Principles of the commercial hs-cTnT assay and the developed highly sensitive UCL long cTnT assay. Lightnings indicate the major N-terminal and C-terminal cleavage sites of the cTnT molecule. hs-cTnT, high-sensitivity cardiac troponin T; cTnT, cardiac troponin T; UCL, upconversion luminescence; UCNP, upconverting nanoparticle.*

AMI by discriminating between cTnT elevations in AMI and ESRD (9). However, only a fraction of circulating cTnT is present in long forms and consequently, the detection of long cTnT requires particularly high analytical sensitivity. The limit of detection (LoD) and quantitation (LoQ) of the TRF long cTnT assay were 11 ng/L and 25 ng/L, respectively (9). Thus, the TRF long cTnT assay could not reach the sufficient sensitivity to reliably measure long cTnT concentrations in patients with small hs-cTnT elevations.

Upconverting nanoparticles (UCNPs) are attractive labels for the development of highly sensitive immunoassays because they can emit anti-Stokes shifted upconversion luminescence (UCL) by converting low energy near-infrared excitation to high-energy emission at visible wavelengths. UCL can be measured completely without autofluorescence background resulting in the excellent detectability of UCNPs (10). The aim of our recently published study was to develop a novel highly sensitive immunoassay for the detection of long cTnT forms using UCL technology to allow better evaluation of long cTnT as a diagnostic biomarker for AMI (11).

Development of a highly sensitive immunoassay for long cTnT forms

In our recently published study, we developed a novel highly sensitive two-step sandwich-type immunoassay for long cTnT utilizing upconverting nanoparticles (UCNP) as reporters (11). The capture and tracer antibodies were selected to target amino acid residues (aar) 223–242 and 171–190, respectively (9). Thus, the UCL long cTnT assay detects cTnT molecules that are not degraded at the major C-terminal cleavage site at aar 190–223 (Figure 1).

The developed UCL long cTnT assay reached a LoD of 0.40 ng/L and LoQ of 1.79 ng/L, which were approximately 28-fold and 14-fold lower than the respective values of the previous TRF long cTnT assay. Thus, the new UCL long cTnT assay allows more sensitive and precise quantification of long cTnT forms in patients with small hs-cTnT elevations and small fractions of long cTnT (11).

The assay was developed to be used with lithium heparin plasma samples. The long cTnT concentrations measured in EDTA plasma and serum samples were approximately 20% lower compared to matched lithium heparin plasma samples. In addition, the decrease was highly variable among the studied serum samples and therefore, serum is not recommended for use with the assay (11).

Long cTn and troponin ratio discriminate between AMI and ESRD patients

The performance of the UCL long cTnT assay with clinical samples was evaluated with samples from patients with non-ST elevation myocardial infarction (NSTEMI, n=30) and ESRD (n=37) and compared to the commercial hs-cTnT assay (i.e. total cTnT assay). Total cTnT concentrations measured with the commercial hs-cTnT assay did not significantly differ between ESRD patients (median [25^{th} – 75^{th} percentile] 76.0 [50.5–124.5] ng/L) and NSTEMI patients (103.0 [47.3–268.3] ng/L, p=0.144), whereas long cTnT concentrations measured with the UCL long cTnT assay were significantly lower in ESRD patients (2.5 [1.9–3.9] ng/L) than in NSTEMI patients (28.4 [6.4–136.6] ng/L, p<0.001). The troponin ratio calculated by dividing the long cTnT result by the total cTnT result was con-

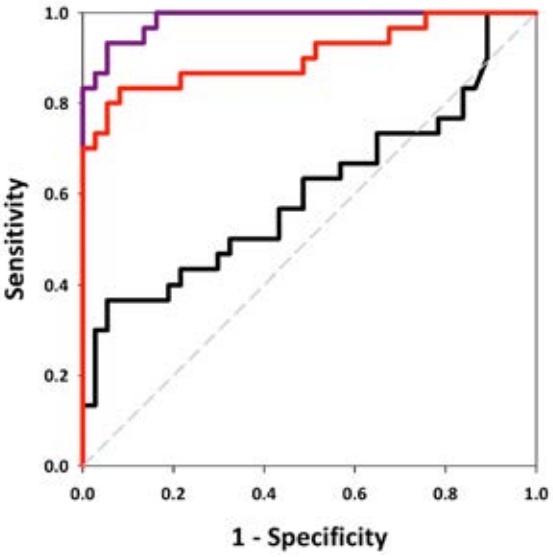

Figure 2. *Receiver operating characteristic curves illustrating diagnostic abilities of total cTnT measured with the commercial hs-cTnT assay (black), long cTnT measured with the UCL long cTnT assay (red) and the troponin ratio of long cTnT to total cTnT (purple) to discriminate between NSTEMI and ESRD patients. cTnT, cardiac troponin T; hs-cTnT, high-sensitivity cardiac troponin T; UCL, upconversion luminescence.*

sequently lower in ESRD patients (3.3% [2.4%–4.5%]) than in NSTEMI patients (21.5% [12.5%–53.3%], p<0.001) (11).

In a receiver operating characteristics curve (ROC) analysis, the developed UCL long cTnT assay exhibited excellent performance in discriminating between patients with NSTEMI and ESRD (Figure 2). The area under the curve (AUC) values for long cTnT and the troponin ratio were 0.905 (95% CI, 0.824–0.985) and 0.986 (95% CI, 0.967–1.000), respectively. The AUC for total cTnT [0.605 (95% CI, 0.461–0.748)] was significantly lower than the AUCs for long cTnT and the troponin ratio (p<0.001) (11).

Conclusions and future perspectives

A highly sensitive long cTnT immunoassay was successfully developed utilizing UCL technology (11). In the future, this novel assay will be a valuable tool for investigating cTnT fragmentation in various patient groups and assessing the full potential of long cTnT as a biomarker for AMI.

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Eldjarn Prize Competition 2024

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The Lorentz Eldjarn Prize competition was held for the sixth time in connection with the 39th Nordic Congress in Clinical Chemistry, which took place on September 17th, 2024, in Stockholm. The prize is funded by the Lorentz Eldjarn Fund, established through a generous donation from Professor Lorentz Eldjarn and his wife Torunn in 2009. The purpose of the prize is to stimulate Nordic publications in the journal Scandinavian Journal of Clinical and Laboratory Investigation (SJCLI), where Eldjarn was editor-in-chief for 12 years.

The picture was generated by Adobe Firefly.

The prize is awarded every two years during the Nordic Congress in Clinical Chemistry. A competition is organized where a committee comprising SJCLI editors selects three articles from the 20 most cited in the five years preceding the congress. To be eligible for nomination, at least one of the article's authors must be affiliated with a research institution in a Nordic country. For the 2024 competition, the prize committee, consisting of Tuija Männistö, Nicolai Wewer Albrechtsen, Henrik Zetterberg, Ann Helen Kristoffersen, and Jens Petter Berg, selected the following three articles among the most cited in the period 2019-2023:

- Anders Larsson, Jonas Tydén, Joakim Johansson, Miklos Lipcsey, Maria Bergquist, Kim Kultima, Aleksandra Mandic-Havelka. Calprotectin is superior to procalcitonin as a sepsis marker and predictor of 30-day mortality in intensive care patients. Scand J Clin Lab Invest. 2020;80:156-161.
- Claus Vinter Bødker Hviid, Cindy Soendersoe Knudsen, Tina Parkner. Reference interval and preanalytical properties of serum neurofilament light chain in Scandinavian adults. Scand J Clin Lab Invest. 2020;80:291-5.
- Anna Åkesson, Veronica Lindström, Ulf Nyman, Magnus Jonsson, Magnus Abrahamson, Anders Christensson, Jonas Björk, Anders Grubb. Shrunken pore syndrome and mortality: a cohort study of patients with measured GFR and known comorbidities. Scand J Clin Lab Invest. 2020;80:412-22.

The competition for first, second, and third prize of DKK 100 000, DKK 50 000, and DKK 30 000 respectively, was conducted as a seminar at the congress in Stockholm, where the authors had 25 minutes to present their articles to the congress participants and

a prize committee consisting of SJCLI editors. There were three excellent presentations of high scientific quality. The committee faced a great challenge in ranking the presentations and concluded with the following order for first, second, and third prize:

1st prize

Anna Åkesson, Veronica Lindström, Ulf Nyman, Magnus Jonsson, Magnus Abrahamson, Anders Christensson, Jonas Björk, Anders Grubb. *Shrunken pore syndrome and mortality: a cohort study of patients with measured GFR and known comorbidities.*

Anna Åkesson

Anders Christensson

Anders Grubb

1. Anders Christensson, Skåne University Hospital, Lund, and Lund University, Sweden, on behalf of first author Anna Åkesson.
2. Anders Larsson, Uppsala University Hospital, Sweden.
3. Claus Vinter Bødker Hviid, Aarhus University Hospital, Denmark.

The prizes, with diplomas as visible proof, were awarded to the winners later in the afternoon at the welcoming reception organized by the congress in connection with the opening. A summary of the winners' articles in SJCLI is provided below.

The article focuses on the relatively high glomerular sieving coefficients for proteins sized between 10–30 kDa in both human and rat kidneys, with values ranging from 0.07 to 0.9. These high sieving coefficients, alongside the significant production of ultrafiltrate, suggest that small peptides and proteins (≤30 kDa) are predominantly catabolized by the kidneys, resulting in a high turnover rate. For instance, at least 85% of cystatin C catabolism occurs in the kidneys.

The article raises an important question: does a reduction in the renal excretion of small molecules

Claus Vinter Bødker Hviid (3rd prize winner), Anders Larsson (2nd prize winner) and Jens Petter Berg (managing editor, Scand J Clin Lab Invest), holding the 1st prize winner´s diploma. Unfortunately, Anders Christensson had to leave before the prize ceremony.

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always correlate with a similar reduction in the excretion of 10–30 kDa molecules? Invasive clearance studies show that this correlation does not always hold. For example, studies in pregnant females and patients with diabetic nephropathy demonstrate selective reductions in the renal clearance of larger molecules (e.g., 10–30 kDa proteins) without a corresponding decrease in smaller molecules' clearance. This pattern leads to the hypothesis of "shrunken pore syndrome" (SPS), where glomerular pore size selectively reduces, affecting larger molecules more.

The authors propose that a simple method to identify this size-selective reduction is to compare the cystatin C-based estimate of GFR ($eGFR_{CYS}$) with the creatinine-based GFR ($eGFR_{CR}$). If the $eGFR_{CYS}$ /$eGFR_{CR}$ ratio is below 0.60 or 0.70, it may indicate SPS, which has been associated with an increase in long-term mortality and morbidity. The present study aimed to explore the association between SPS and mortality while accounting for patient characteristics and disease history.

The cohort consisted of patients undergoing their first GFR examination as part of the Lund Cystatin C Standardization (LCS) cohort, created to develop a new cystatin C-based GFR equation (the CAPA equation). The final sample size represented 2781 unique patients. GFR in this study was measured using plasma clearance of iohexol (mGFR). Cystatin C levels were determined using a particle-enhanced immunoturbidimetric method, while creatinine was measured with an enzymatic colorimetric assay, both calibrated against international reference standards. Participants' survival and cause-specific death data were followed up until February 28th, 2016, using linkage to the Swedish population and cause of death registers. Diagnoses were categorized into cancer, cardiovascular disease (CVD), diabetes mellitus (DM), and chronic kidney disease (CKD).

The study observed an overall mortality rate of 37.7% over a 5.6-year median follow-up period among the 2781 adults. The $eGFR_{CYS}$ /$eGFR_{CR}$ ratio distribution showed that lower ratios correlated with higher mortality. Specifically, an $eGFR_{CYS}$ /$eGFR_{CR}$ ratio below 0.70 significantly increased mortality

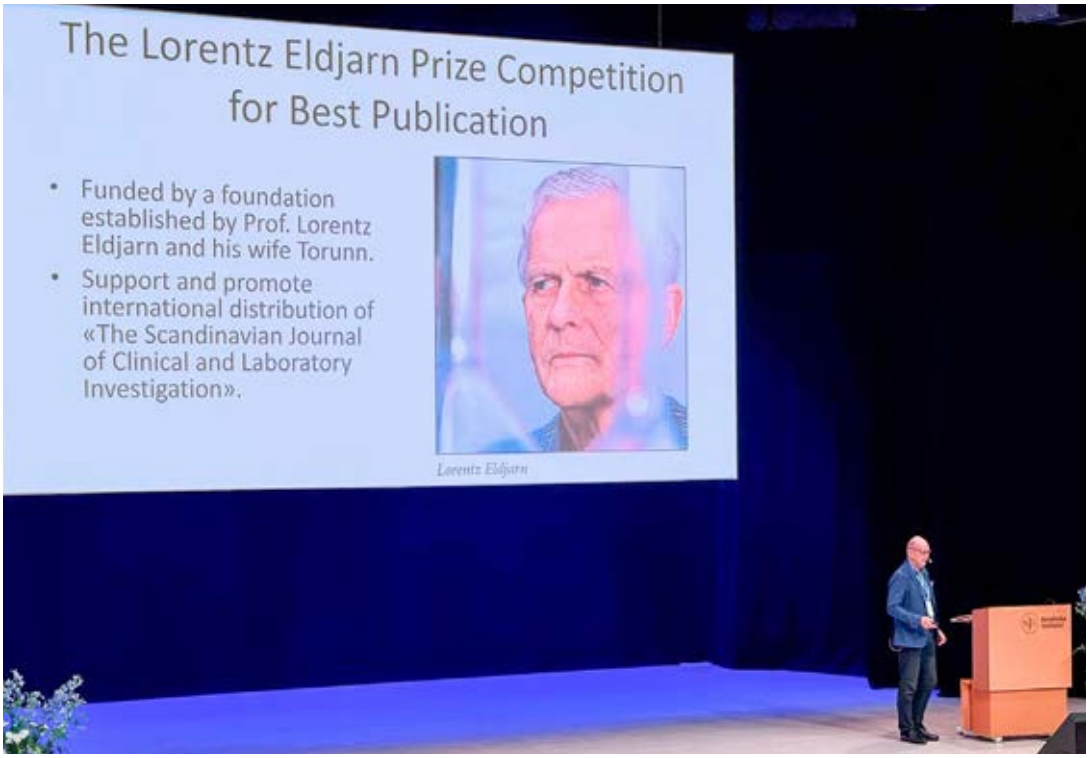

Photo: Per Bjellerup.

risk (adjusted HR 3.0). This increased mortality was also observed in sub-cohorts with normal mGFR and without any diagnosis.

Conducting additional analyses using different $eGFR_{CYS}$ /$eGFR_{CR}$ ratio intervals confirmed a progressive increase in mortality with decreasing ratios. The study also verified similar results using alternate GFR-estimating equations (CKD-EPI and FAS). Lower $eGFR_{CYS}$ /$eGFR_{CR}$ ratios were associated with higher mortality for cancer, CVD, DM, and CKD, albeit with more variability in less frequent causes of death. In a sub-cohort of 1049 individuals without cancer, CVD, DM, or CKD, the all-cause mortality increased significantly as the $eGFR_{CYS}$ / $eGFR_{CR}$ ratio decreased (HR 3.7). Similar trends were observed in other sub-cohorts, including those with normal mGFR and those with neither diagnoses nor reduced mGFR.

The prevalence of SPS in the total cohort was found to be 23%. In sub-cohorts, it ranged from 12% to 17%. The highest HR for mortality was found in the healthiest sub-cohort with normal mGFR and no diagnoses, indicating that SPS likely represents a distinct pathophysiological process.

Previous studies have shown that combined cystatin C- and creatinine-based eGFR estimates are more reliable than estimates based on a single marker. Elevated levels of cystatin C have been more strongly associated with increased mortality compared to elevated creatinine levels. The proposed new kidney disorder, SPS, characterized by a higher cystatin C/ creatinine concentration ratio, might explain the superior predictive value of cystatin C for mortality. The pathophysiology behind SPS involves a selective reduction in pore size in the glomerular membrane, preferentially impairing the filtration of larger molecules while not affecting smaller ones like creatinine.

The study underscored that current CKD classifications might miss a significant portion of individuals with serious kidney disorders who do not display reduced GFR or albuminuria but may still have SPS, suggesting that $eGFR_{CYS}$ /$eGFR_{CR}$ ratios should be considered in diagnostics.

While the data quality in the Swedish patient register is high, some baseline disease history misclassifications are likely. The study also cannot definitively attribute causality between SPS and mortality, though significant associations were found. Additionally, as the study involved a specific patient cohort with varied medical reasons for GFR measurement, the results may not be generalizable to broader populations.

This detailed study reinforced the significance of SPS as a new, pathophysiologically distinct kidney disorder with severe implications for patient mortality, emphasizing the need for its inclusion in the optimal classification and stratification of kidney diseases.

2nd prize

Anders Larsson, Jonas Tydén, Joakim Johansson, Miklos Lipcsey, Maria Bergquist, Kim Kultima, Aleksandra Mandic-Havelka. *Calprotectin is superior to procalcitonin as a sepsis marker and predictor of 30-day mortality in intensive care patients.*

Infections result in over 10 million deaths per year, with sepsis affecting between 3 to 10 per 1000 people annually in industrialized countries. Sepsis is the leading cause of ICU admissions and ICU deaths. The incidence and prevalence of sepsis have been increasing. Early identification and treatment are critical to reducing mortality and morbidity.

Sepsis diagnosis is challenging due to non-specific symptoms, and delays in treatment significantly increase mortality. Biomarkers play a crucial role in detecting sepsis and assessing its severity. They help differentiate between bacterial, viral, and fungal infections, which require distinct treatments. C-reactive protein (CRP) and procalcitonin (PCT) are widely used sepsis biomarkers. CRP is mainly an inflammation marker and its specificity in sepsis has been questioned. PCT has been proposed as more specific and a better prognostic marker than CRP, but this has also been debated.

Neutrophil granulocytes react to bacterial infections, releasing calprotectin upon activation. Calprotectin, consisting of S100A8 and S100A9 subunits, quickly increases in response to infection. It has been suggested as a marker for acute appendicitis, rheumatoid arthritis, and sepsis. This study aimed to compare calprotectin and PCT as markers for sepsis and 30-day mortality in ICU patients.

This prospective observational study took place in an eight-bed ICU at Östersund hospital, Sweden. The study included all patients admitted between February 2012 and January 2013, excluding those transferred from other ICUs or under 18 years old.

Blood samples were collected upon ICU admission and during the following two days. Samples were processed and stored at –80°C until analyzed. PCT was measured using a commercial ELISA, and calprotectin was measured using particle-enhanced turbidimetric assay (PETIA) on a Mindray chemistry analyzer. Sepsis was defined by Sepsis-3 criteria.

271 patients were included: 77 with sepsis, 33 with trauma, 78 with other medical conditions (OMC), and 83 with miscellaneous conditions. Sepsis and non-sepsis groups were compared using various statistical tests. Calprotectin levels were significantly higher in sepsis patients compared to trauma, OMC, and miscellaneous patients. Higher calprotectin levels were also observed in non-survivors at 30 days. PCT levels did not significantly differ between groups or outcomes. ROC analysis showed better discrimination for calprotectin compared to PCT. Calprotectin's sensitivity for distinguishing sepsis from non-sepsis, trauma, OMC, and mortality was high and remained an independent predictor for sepsis after adjusting for age, sex, SAPS3, and SOFA scores.

Neutrophils play a vital role in responding to infections, and calprotectin, as a neutrophil activation marker, effectively reflects this response. The study found calprotectin to be a superior biomarker compared to PCT for identifying sepsis and predicting 30-day mortality. The PETIA method for calprotectin allowed rapid analysis, making it suitable for acute conditions like sepsis. The study was limited by including only 59 severe sepsis patients and being conducted in a single ICU with a purely Caucasian population, reducing the generalizability of the results.

Calprotectin outperformed PCT in distinguishing sepsis patients from non-sepsis patients and predicting 30-day mortality, highlighting its potential as a valuable biomarker for clinical use in ICU settings.

3rd prize

Claus Vinter Bødker Hviid, Cindy Soendersoe Knudsen, Tina Parkner. *Reference interval and preanalytical properties of serum neurofilament light chain in Scandinavian adults.*

Neurofilament light chain (NfL) is an intracellular protein specific to neurons, predominantly found in the axons of myelinated neurons. It is released into the extracellular environment following neuronal injury and has proven to be a reliable and versatile biomarker for neuronal decay. Studies have highlighted NfL's prognostic and predictive potential across various neurodegenerative diseases, traumatic brain injuries, anoxic states such as cardiac arrest or stroke, and even mild repetitive head injuries.

Initial quantitative studies focused on measuring NfL levels in cerebrospinal fluid (CSF), where levels are detectable in healthy individuals. However, advancements in ultra-sensitive technologies like the Single Molecule Array (Simoa™) have enabled the measurement of NfL in peripheral blood, demonstrating a strong correlation between CSF and plasma NfL levels. Measuring NfL in blood offers advantages including lower resource requirements, improved patient comfort, and greater feasibility. Understanding the reference interval and pre-analytical properties of NfL can enhance its clinical utility.

This study used the NF-light kit on the Simoa HD-1 platform under quality control to establish reference intervals for serum NfL in a Danish population and reported key pre-analytical properties of circulating NfL.

Reference subjects were recruited from blood donors and outpatients at Aarhus University Hospital. Blood donors, aged 18-67 years, were volunteers meeting strict health criteria. Outpatients above 50 years old, referred mainly from general practitioners, were included if they didn't have diabetes, dementia, stroke, or referrals from neurology/neurosurgery departments. Blood samples were also collected for stability testing and freeze-thaw studies. Paired serum and CSF samples were obtained from excess clinical specimens tested for Borrelia burgdorferi antibodies.

Blood samples were drawn from the antecubital vein into EDTA or serum tubes, processed at room temperature, and centrifuged before being stored at –80°C. CSF samples were collected via lumbar puncture, processed, and stored at –20°C. Stability testing involved storage of serum samples at room temperature and repeated freeze-thaw cycles. The correlation between serum and CSF NfL levels as well as the comparison between EDTA plasma and serum NfL levels were analyzed.

NfL was measured using the NF-light® assay on the Simoa™ HD-1 platform. Internal controls and an external quality program for CSF biomarkers were employed. Samples were analyzed in duplicate, and

results were reported as the mean of the duplicates.

The reference interval was established in accordance with CLSI guidelines, with outliers detected by Dixon D/R ratio and decisions on partitioning based on specific recommendations. Age and gender effects on NfL levels were analyzed using regression models.

The intermediate precision for serum controls (4.4 ng/L and 18.1 ng/L) demonstrated coefficients of variation (CV) of 12.9% and 11.2%, respectively. The average CV of duplicates was 2.7%, and different lots showed variations of 10.2% and 8.0% at specified average levels. External controls remained within acceptable limits.

342 reference subjects (170 males, 172 females) aged 18–87 years were included. Serum NfL levels showed a strong association with age but were independent of sex. The correlation between serum NfL and age improved after logarithmic transformation, leading to a regression formula used to estimate upper reference limits by ten-year intervals.

Serum NfL demonstrated stability after three and seven days at room temperature and after multiple freeze-thaw cycles. Serum NfL levels were higher, and more variable compared to EDTA plasma, but the differences were hardly of clinical relevance. NfL levels in serum and CSF correlated strongly.

This study established an age-dependent reference interval for serum NfL using an ultra-sensitive platform. Serum NfL levels were shown to increase with age but were not affected by gender. Pre-analytical properties supported the use of serum NfL as a stable and feasible biomarker for clinical applications.

The study provided a non-parametric, age-partitioned reference interval for serum NfL and estimated the upper reference limit by decade intervals. It confirmed the favorable pre-analytical properties of serum NfL, supporting its potential as a reliable biomarker for clinical use and further research in patient management.

Summaries of the articles were based on text generated by the large language model gpt.uio.no

Amyloid plaques in Alzheimer´s disease.

Kan kønsspecifikke grænseværdier for troponin forbedre diagnostik af akut myokardie infarkt hos kvinder?

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Siden den første konsensus definition for snart 25 år siden har troponin fungeret, som den biokemiske guldstandard for diagnosen akut myokardieinfarkt (AMI) (1). I samme forbindelse valgte man at definere den øvre grænseværdi ud fra 99.-percentilen blandt raske med et rationale om, at det approksimerede 3 standard deviationer fra gennemsnittet (2). Disse definitioner har ikke ændret sig siden hen, og den seneste konsensus definition i 2019 tilføjede yderligere begrebet myokardieskade (myocardial injury), som er opfyldt ved en hvilken som helst måling over 99.-percentilen (3). For at opfylde kriterierne for diagnosen AMI, skal der samtidigt observeres en stigning eller fald i koncentrationen af troponin og mindst ét klinisk tegn, såsom brystsmerter eller elektrokardiografiske ændringer.

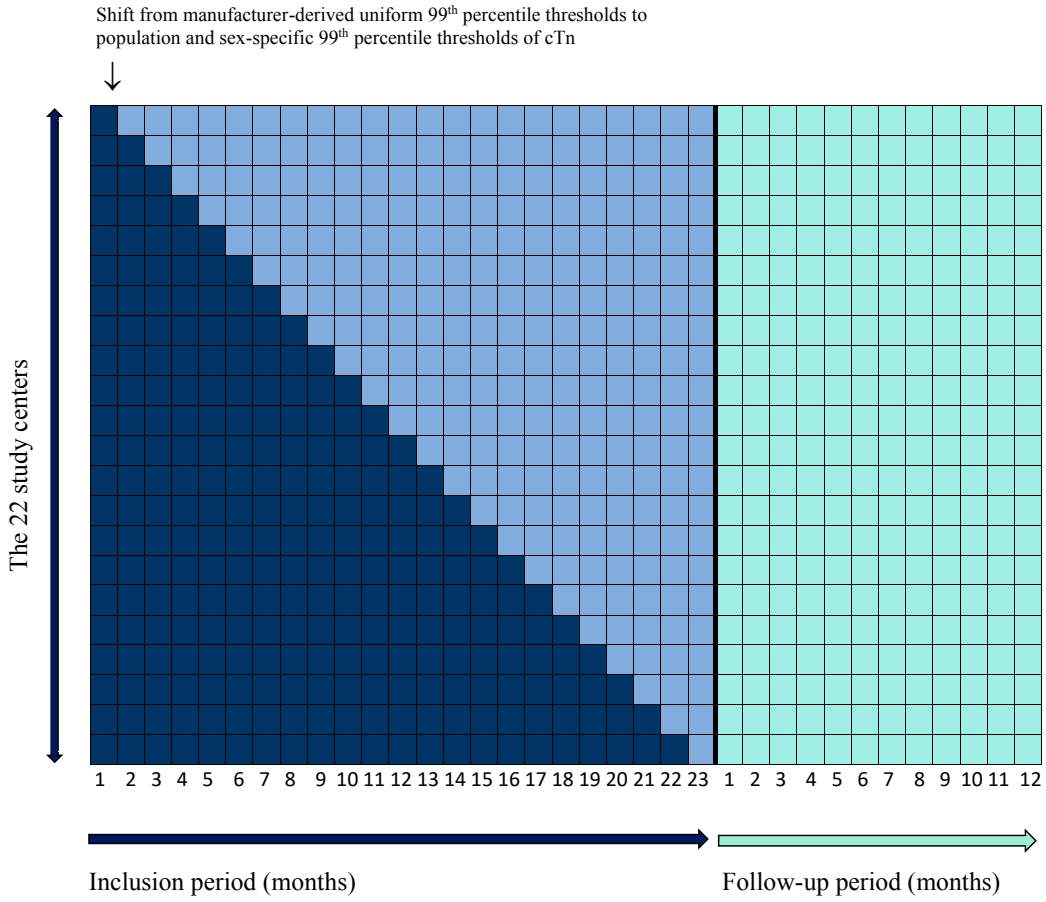
Kvinder og hjertesygdom

Trods de generelle fremskridt i behandlingen af hjertesygdom, er det stadig den hyppigste dødsårsag blandt kvinder med omkring 35% af alle dødsfald (4). Kvinder har en tendens til at debutere med mere atypiske symptomer på hjertesygdom, og kvinder med AMI modtager sjældnere relevante undersøgelser, behandlinger og interventioner end mænd (5,6). Derfor har kvinder også en dårligere prognose efter et AMI end mænd. Disse erkendelser har medført et betydeligt fokus på at forbedre diagnostik og behandling for kvinder med hjertesygdom (7).

Kønsspecifikke grænseværdier

Siden indførslen af troponin er det vist flere gange, at der er betydelig forskel på den normale koncentration af troponin i blodet for kvinder og mænd (8–10). Dette menes at skyldes forskel i forholdet mellem hjerte- og kropsstørrelse for mænd og kvinder (11).

Der er flere observationelle studier, der har undersøgt brugen af kønsspecifikke grænseværdier for troponin. De fleste af disse har undersøgt retrospektivt, hvor mange der kunne re-klassificeres fra ikke-AMI til AMI ved indførelse af kønsspecifikke værdier. Studierne har vist at andelen, der kan re-klassificeres i høj grad afhænger af hvilket assay af troponin man bruger. Et britisk studie, der brugte Abbotts high sensitivity assay, viste en stigning i prævalensen af AMI blandt kvinder fra 11% til 22% ved skifte fra forrige generation af troponin assays til high sensitivity assays med kønsspecifikke grænseværdier (12). Studiet viste igen at kvinder blev behandlet mindre end mænd og at kvinder i den re-klassificerede gruppe havde lige så høj risiko for at opleve et nyt AMI eller dø som kvinder med AMI defineret ved de gamle grænseværdier. Omvendt viste et lignende studie med brug af Roches high sensitivity troponin T assay at effekten af kønsspecifikke grænseværdier var marginal (13). Samlet førte disse studier til anbefalingen om at skifte fra uniforme til kønsspecifikke grænseværdier for troponin i forbindelse med den 4. konsensus definition af AMI (3).



Figur 1. **Studiedesign for DANSPOT-studiet, en landsdækkende implementering af populations- og kønsspecifikke diagnostiske grænseværdier for troponin ved anvendelse af et "stepped-wedge"-design.** *Med et månedligt interval har hvert center implementeret de nye populations- og kønsspecifikke diagnostiske grænseværdier. Efter udskrivelse fra den primære indlæggelse følges patienterne individuelt i 12 måneder. cTn angiver kardiel troponin. (Ref.15)*

Mangelfuld evidens for effekt

Til trods for de nye anbefalinger om kønsspecifikke grænseværdier viste en undersøgelse i 2019 af omkring 2000 centre i 23 lande, at kun omkring en femtedel af alle centre med high sensitivity assays brugte kønsspecifikke grænseværdier (12). Heraf havde ingen danske hospitaler på daværende tidspunkt indført ændringen. Det første randomiserede studie af high sensitivity troponin med kønsspecifikke grænseværdier, The High-Sensitivity Troponin in the Evaluation of patients with suspected Acute Coronary Syndrome trial, High-STEACS, udkom i 2018 (7). I High-STEACS studiet indførte man Abbotts high sensitivity troponin assay i et stepped-wedge studie over en række centre i England. I den forbindelse kunne man analysere effekten på kvinder i den relevante gruppe, men på trods af at studiet viste en klar stigning i andelen af patienter diagnosticeret med AMI, og at denne stigning var 5 gange højere for kvinder end mænd, ledte dette ikke til en forskel i det primære endepunkt, som var død eller nyt AMI (14). Således er der stadig usikkerhed om effekten af at indføre kønsspecifikke grænseværdier.

Formålet med vores studie er derfor at undersøge effekten af at indføre kønsspecifikke grænseværdier for troponin.

DANSPOT-studiet

DANSPOT-studiet (The Danish Study of Sex- and Population-Specific 99th Percentile Upper Reference Limits of Troponin) er et igangværende, nationalt, randomiseret klinisk studie i Danmark, der undersøger, om kønsspecifikke grænseværdier for troponin kan øge diagnostisk præcision og forbedre kliniske udfald hos patienter med AMI for både kvinder og mænd (15,16). Studiets primære hypotese er, at de fælles grænseværdier for troponin, der anvendes globalt, medfører underdiagnosticering af AMI hos kvinder og overdiagnosticering hos mænd. Ved at tilpasse grænseværdierne til kvinders fysiologiske normalniveauer forventes flere kvinder at få en korrekt diagnose og behandling. Samtidig vil de kønsspecifikke grænseværdier for mænd hæves en smule, hvilket vil betyde, at en mindre gruppe mænd, som tidligere overskred den fælles grænseværdi, nu vil falde under den nye kønsspecifikke grænseværdi. Dette forventes at reducere risikoen for unødvendige indgreb og overbehandling blandt mænd.

Studiedesign

1.Bestemmelse af kønsspecifikke 99-percentiler i en rask dansk referencepopulation.

I første del af DANSPOT-studiet blev populations- og kønsspecifikke grænseværdier fastlagt ud fra biobanksdata fra en rask dansk referencepopulation, stratificeret efter køn og alder. Vi valgte at aldersstratificere inklusionen, da undersøgelser har vist, at alder spiller en vigtig rolle i koncentrationen af troponin hos raske såvel som syge (9,11,17,18). Biobanken blev etableret i sommeren 2021, hvor aktive og tidligere bloddonorer blev inviteret til at deltage. Deltagerne blev screenet via et spørgeskema med eksklusionskriterierne hjertesygdom, nyresygdom, diabetes og brug af statin eller acetylsalisyre (som proxy for hjertesygdom). Fra 31. maj til 18. august 2021 indsamledes blodprøver fra 2.287 deltagere i alderen 18-88 år til biobanken. Blodprøverne blev straks analyseret for tegn på ikke-erkendt hjertesygdom, diabetes og nyresygdom ved hjælp af screeningsbiomarkører anbefalet i The International Federation of Clinical Chemistry and Laboratory (IFCC) guidelines (19). NT-proBNP, kreatinin (eGFR) og HbA1c. Alle disse målinger inklusiv troponin I på Siemens Atellica high sensitivity assay blev udført på Herlev-Gentofte Hospital. Resterende blodprøver blev centrifugeret ved 3000 relativ centrifugalkraft i 10 minutter ved 20°C, opdelt i kryorør og derefter opbevaret ved −80°C inden videre analyse. Efterfølgende blev de frosne plasmaprøver sendt til repræsentative klinisk biokemiske laboratorier til analyse på yderligere fire troponin-assays (Siemens Dimension Vista high sensitivity troponin I på Sjællands Universitetshospital; Roche Diagnostics Elecsys 2010 troponin T på Rigshospitalet; Abbott Alinity STAT high sensitivity troponin I på Sydvestjysk Sygehus; Ortho Clinical Diagnostics VITROS high sensitivity troponin I på Rigshospitalet - Glostrup). Screeningen førte til eksklusion af 951 deltagere, hvis screeningsbiomarkører lå uden for de fastsatte grænser i henhold til IFCC guidelines (19). De fleste af eksklusionerne (n=944) skyldtes nedsat nyrefunktion (eGFR <90 ml/min/1.73m^2). Den endelige referencepopulation bestod af 720 kvinder og 605 mænd.

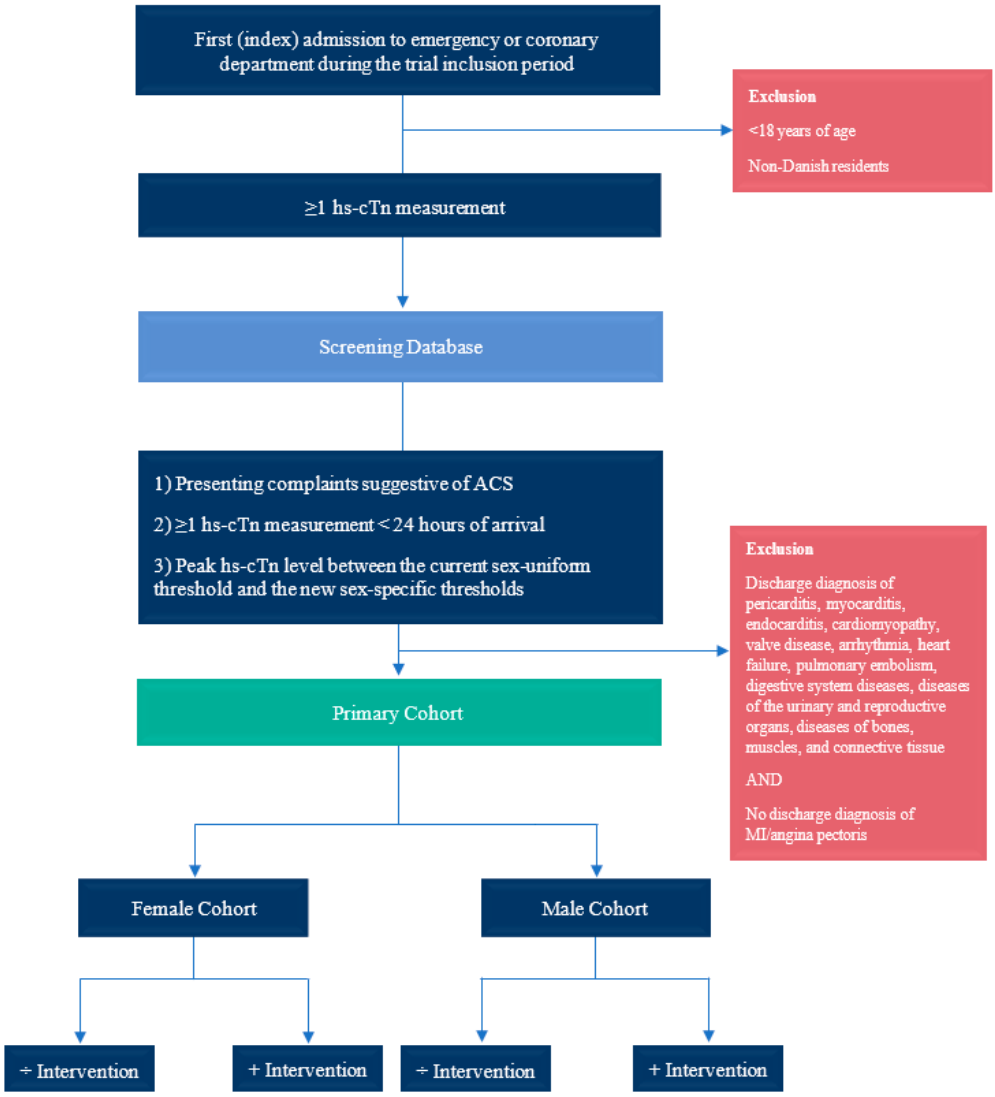
De nye populations- og kønsspecifikke grænseværdier for troponin blev beregnet ved hjælp af den non-parametrisk metode som anbefalet af IFCC Task Force on Clinical Applications of Bio-Markers (19,20).

2. National cluster-randomiseret implementering af kønsspecifikke 99-percentiler.

Anden del af DANSPOT-studiet udførtes som et landsdækkende, cluster-randomiseret forsøg ved brug af et stepped-wedge design. Her implementeredes de nye kønsspecifikke grænseværdier for troponin trinvist på 22 af Danmarks 23 hospitaler, der behandler patienter med AMI. Hvert center (cluster) blev randomiseret til forskellige starttidspunkter med et månedligt interval. Implementeringen begyndte på det første center den 1. april 2022 og blev fuldført på det sidste center den 1. januar 2024. Denne trinvise implementeringsmetode gjorde det muligt at skifte fra den standardiserede fælles grænseværdi til kønsspecifikke grænseværdier på forskudte tidspunkter. Perioden før implementering for det enkelte center vil fungere som kontrolfase, hvor de fælles grænseværdier blev anvendt, mens perioden efter overgangen vil fungere som interventionsfase, hvor de nye kønsspecifikke grænseværdier blev taget i brug i klinisk praksis. Designet tillader en systematisk sammenligning af kliniske udfald før og efter ændringen for patienter med AMI, med mulighed for at tage højde for sæsonvariationer og andre potentielle confoundere.

Tidslinje

Dataindsamlingen til DANSPOT-studiet blev plan-



***Figur 2.* Flowchart for selektion af den primære kohorte til analyse.** *Den nuværende fælles grænseværdi og de nye kønsspecifikke grænseværdier er assay-specifikke for hvert center. ACS angiver akut koronart syndrom; Hs-cTn, høj-sensitivt kardiel troponin-assay; og MI, myokardieinfarkt. (Ref. 15)*

lagt til at vare over en periode på tre år, hvoraf 23 måneder blev afsat til at inkludere hospitalscentrene og 12 måneder til opfølgning af patienterne. For at sikre en tilpasningsperiode på hvert center udelukkes data fra den første måned efter implementering af de nye grænseværdier. Denne justering har forlænget inklusionsperioden med en måned, og den endelige inklusion blev dermed afsluttet den 29. februar 2024.

Alle inkluderede patienter følges i 12 måneder fra udskrivelsen efter deres første (index-) indlæggelse, hvor forekomsten af studiets primære endepunkt registreres. Hele opfølgningsperioden afsluttes den 1. marts 2025, hvorefter adjudikation af det primære endepunkt for primærkohorten og dataanalyse påbegyndes. De første resultater fra studiet forventes publiceret i første halvdel af 2026.

Primærkohorten og primære endepunkt

Alle patienter over 18 år, der i inklusionsperioden præsenterer sig med symptomer på AKS og har fået målt troponin inden for 24 timer efter ankomst, registreres i en screeningsdatabase. Herfra udvælges primærkohorten, som omfatter de kvinder og mænd, der forventes at blive mest påvirket af overgangen til de nye kønsspecifikke grænseværdier. Disse patienter defineres ved: 1) symptomer eller diagnose ved ankomst, der tyder på AKS, 2) mindst én troponin-måling indenfor 24 timer efter indlæggelse, og 3) en peak troponin-værdi mellem den assay-specifikke fælles grænseværdi, og de nye kønsspecifikke grænseværdier.

Det primære endepunkt er sammensat og inkluderer forekomst af myokardieinfarkt, ikke-planlagt revaskularisering og død af alle årsager inden for 12 måneder efter udskrivning fra index-indlæggelsen. Forekomsten af det primære endepunkt analyseres separat for mænd og kvinder i primærkohorten før og efter indførslen af de nye kønsspecifikke grænseværdier. For patienter i primærkohorten, der genindlægges i løbet af opfølgningsperioden, vurderes diagnoserne af en endepunktskomité, der identificerer type 1, type 2 eller type 4b AMI. Endepunktskomitéen, der består af to kardiologer fra hver af Danmarks fem regioner, gennemgår patientjournaler uafhængigt, og en tredje kardiolog konsulteres ved tvivl eller uenighed.

Sekundære endepunkter omfatter forekomsten af myokardieskade og AMI separat, antal koronarangiografier eller koronar CT-skanninger uden revaskularisering, antal revaskulariseringer (PCI og CABG), ikke-planlagte revaskulariseringer, behandling med acetylsalicylsyre, andre trombocythæmmere og statiner, genindlæggelse inden for 12 måneder, indlæggelseslængde samt død af alle årsager separat.

Perspektivering

Anvendelsen af en fælles diagnostisk grænseværdi for troponin har været foreslået som en medvirkende faktor til både underdiagnosticering og underbehandling af kvinder med myokardieinfarkt. Indførslen af kønsspecifikke grænseværdier forventes at forbedre den diagnostiske præcision, hvilket potentielt kan give flere kvinder adgang til nødvendige undersøgelser og korrekt behandling, herunder revaskularisering og livslang profylaktisk behandling. Samtidig forventes en reduktion i andelen af overdiagnosticerede mænd, hvilket kan mindske antallet af unødvendige procedurer og behandlinger, der ellers belaster sundhedsvæsenet og påvirker patienterne.

Konklusion

DANSPOT-studiet er det første af sin art i Danmark og blandt få internationale studier, der undersøger effekten af kønsspecifikke grænseværdier for troponin i et randomiseret design. Hvis studiet viser, at kønsspecifikke grænseværdier forbedrer den diagnostiske præcision for kvinder uden at forårsage underbehandling af mænd, kan det danne grundlag for at indføre kønsspecifikke grænseværdier som standard i Danmark og muligvis globalt. Studiet forsøger at imødekomme et underbelyst behov for kønsdifferentiering i hjertediagnostik og søger at fremme en mere præcis og ligestillet tilgang til behandling af AMI for begge køn.

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Greetings from the Nordic preanalytical scientific working group

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In the beginning of the year, the Nordic preanalytical scientific working group arranged a competition to get more preanalytical stories for our website. We received eight stories and voted on these to select a winner. The winner story came from Norway, and the author was, as promised, granted a free entrance to the NFKK Congress in Stockholm that was held in September this year.

The winning story was as follows

Case
43-year-old with known type 2 diabetes mellitus admitted to the emergency department with suspected diabetic ketoacidosis. Severe metabolic acidosis was confirmed by the blood gas analyses:

Arterial blood gas
↓↓ pH 6,82
↓↓ Base excess -28,2 mmol/L (± 3)
↑ Anion gap 24,4 mmol/L (6-17)
↑ Glucose 33 mmol/L
(↑) Creatinine 112 µmol/L
(↑) Lactate 5,0 mmol/L (0-2,5)

Venous blood analyses
↓↓ Hb 5,0 g/dL (prehospital Hb was 17, later 12-13)
↑ Glucose 12,9 mmol/L (with the comment: lipemic sample, may give falsely elevated result)
↓↓ Creatinine 32 µmol/L
↑↑ Triglycerides 39,4 mmol/L
↑↑ P-Osmolality 637 (280-300)
↑↑ S-Phosphate 12,3 mmol/L (0,75-1,65)

Questions
1. Why was Hb low, and why was creatinine and glucose lower in the venous sample than in the arterial blood gas?
2. Explanations for the elevated osmolality and phosphate?
3. Can lipemia explain these results?

Explanations
1. Dilution of the venous blood sample from intravenous solution
2. Contamination with the intravenous solution Tribonat
3. Many analyses are affected by lipemia, but not those mentioned

The patient was treated with Tribonat, an intravenous solution used for treatment of metabolic acidosis. Tribonat contains hypertonic electrolyte concentrations with an osmolality of around 800 mosmol/kg and high phosphate concentration of 20 mmol/L. The venous blood sample was drawn from the same arm as the i.v. infusion, which resulted in a ≈ 3:1-dilution

of the blood sample with Tribonat (roughly estimated from the differences in Hb, glucose and creatinine results). Sample dilution with Tribonat explains the low Hb, creatinine and glucose results in the venous sample, and also the highly elevated osmolality and phosphate concentration.

What about lipemia? Several other tests of this patient were difficult to interpret because of the lipemia, which added to the confusion of the blood test results. In fact, the triglycerides were also falsely low because of dilution, so probably the real triglyceride concentration was more than 100 mmol/L.

Congratulations to Gunnhild Kravdal from Akershus university hospital in Norway!

The educational preanalytical stories are available to everyone and can be found on NFKK's website: https://www.nfkk.org/wp-content/uploads/Preanalytical-cases_2024.pdf

The picture was generated by Adobe Firefly.

The Nordic preanalytical scientific working group

The working group supported by NFKK has the purpose to act as an advisor for the Nordic clinical chemistry societies on different aspects. The group aims to promote the importance of the quality of the preanalytical phase in the Nordic countries by conducting surveys to assess the current practices. It aims to provide recommendations, write opinion letters, and it has also organized several sessions on preanalytical issues. The group members are:

- Mads Nybo, Dept. of Clinical Biochemistry, Odense, Denmark
- Gunn B. Kristensen, Norwegian Quality Improvement of laboratory examinations (Noklus), Bergen, Norway
- Britta Willman, Laboratory medicine, clinical chemistry, University Hospital Umeå, Sweden
- Jonna Pelanti, Labquality, Finland

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"The Professional Role of a Clinical Biochemist / Laboratory Doctor"

September 15th - 17th 2025 in Copenhagen

Objective of the course	The overall topic is to introduce various professional roles in clinical biochemistry – and to discuss what is important when searching for a professional role. Various examples of professional roles of clinical biochemists/laboratory doctors are presented, either by lecturers sharing their personal academic road or by lecturers presenting how they manage important tasks being a specialist in clinical biochemistry. There are 3 sessions with topics within basic clinical biochemistry, laboratory operation and development and leadership and communication. Most lecturers are well known experts within their specific field and will present themselves and their professional role in combination with their specific topic. **After the course you have** • Achieved knowledge regarding a wide range (arrays) of professional opportunities that exist in clinical biochemistry and the diversity within the specialty • Improved your ability to be critical and reflective in transitions from one role to another. • Obtained inspiration towards your own possibilities • Improved your ability to ensure an efficient laboratory operation and to manage important stakeholders In the end the course should induce the participants to reflect on their own role and bring them one step ahead in that process.
Programme	**Day 1:** Goldmining in clinical biochemistry **Day 2:** Laboratory operation and development **Day 3:** Leadership and communication Detailed programme will follow.
Teaching methods	The participants must expect some preparation before the course. **The course consists of:** • Lectures • Groupwork • Presentations from/in groups
Participants	The course is for MD's in specialist training for clinical biochemistry. *Depending on the number of participants there may be openings for PhD students or (bio)chemists. The Course is not approved in the specialist education for (bio)chemist in Denmark.
Dates	**Registration deadline:** July 15th 2025 **Course dates:** September 15th - 17th 2025 **Arrival for participants:** September 14th or in the morning September 15th 2025

Registration	Send the following information by e-mail to Debbie Norring-Agerskov (debbie.agerskov@gmail.com) Name: MD: yes/no If not MD, specify: E-Mail address: Position: Department: Hospital: Country: **Hotelroom:** Please note if accommodation is needed all three days: September 14th - 15th September 15th - 16th September 16th - 17th
Location	Copenhagen – details will follow.
Price	Dkr 7000,- including breakfast, lunch and accommodation (Dkr 3500 for accommodation and Dkr 3500 for the course)
Questions	**Please contact course coordinators:** Nete Hornung Department of Clinical Biochemistry Gødstrup Hospital DK-7400 Herning Denmark e-mail: nete.hornung@goedstrup.rm.dk Linda Hilsted Department of Clinical Biochemistry Rigshospitalet DK-2100 Copenhagen Ø Denmark

Kurs:

Statistik och kvalitetsarbete inom laboratoriemedicin 2025

Ola Hammarsten
Kursledare, overläkare och ämnesprofessor
hammarstenlabstat@outlook.com

Målgrupp: Kursen vänder sig till läkare, kemister, mikrobiologer, ingenjörer samt andra inom sjukvård, forskning och industri som arbetar med kvalitets- och utvecklingsarbete, och/eller har intresse för praktisk användning av statistik i dagliga arbetsuppgifter. Kursen är kvalitetssäkrad av Svensk Förening för Klinisk Kemi (SFKK) och kan tillgodoräknas som en del av specialistutbildningen inom laboratoriemedicinska specialiteter:

- Klinisk kemi
- Klinisk immunologi och transfusionsmedicin
- Klinisk mikrobiologi
- Klinisk farmakologi

Intresseanmälan för att säkra kursplats:
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Språk: Svenska

Kurstid: Måndag till Fredag kl. 9:00 – 17:00,
2025-03-24 - 2025-03-28

Pris: 9500 SEK

Plats: Campus Johanneberg – Chalmers,
Sven Hultins Plats 5, Göteborg
https://www.aworkinglab.se/johanneberg/

Kursinnehåll: Praktisk statistik i det dagliga arbetet på medicinska laboratorier:

1. Referensintervall och handlingsgränser.
2. Interna och externa kvalitetsmål, ackreditering.
3. Intern och extern kvalitetskontroll i praktiken.
4. Mätosäkerhet – beräkning och beskrivning.
5. Validering och verifiering av mätmetoder.
6. Metodjämförelser och interna labb-rapporter.
7. Analysers kliniska användbarhet, inklusive sensitivitet, specificitet, prediktionsvärden, Bayes teorem, ROC-kurvor samt AI-baserade verktyg.
8. Hur de olika t-testen fungerar samt icke-parametriska signifikanstester.

Kursens upplägg: Kursdagarna inleds med en kort föreläsning om dagens ämne. Därefter gruppvis arbete med dagens uppgift, t.ex. referensintervall. Gruppen beräknar utifrån data i Excel, läser och tittar på filmer på kursens webportal via Hypocampus. Under grupparbetet förbereder gruppen en 15-minuters miniföreläsning om referensintervall samt resultat från beräkningar. Kursdagarna avslutas med att grupperna presenterar sina miniföreläsningar för varandra i grupp-par under examinerande handledning.

Förkunskaper: Grundläggande kunskaper i Excel och PowerPoint eller motsvarande program. Övergripande genomgång av kursens webportal som blir tillgänglig efter kursanmälan.

Kurslitteratur: Kursen sammanfattar följande kapitel i Tietz Fundamentals of Clinical Chemistry and Molecular Diagnostics, 7th Edition:

- Kapitel 2: Statistical Methodologies in Laboratory Medicine
- Kapitel 6: Quality Control of the Analytical Examination Process
- Kapitel 7: Standardization and Harmonization of Analytical Examination Results
- Kapitel 8: Biological Variation and Analytical Performance Specifications
- Kapitel 9: Establishment and Use of Reference Intervals

Doktorsavhandling:

Biomarkörer vid diagnostik av hepatocellulärt carcinom

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Bakgrund

Hepatocellulärt carcinom (HCC) är den vanligaste formen av primär levercancer i världen. Globalt sett år 2020 var levercancer den sjunde vanligaste cancerformen och den näst vanligaste orsaken till cancerrelaterad död (1).

Tidig HCC är ofta asymtomatisk och svår att upptäcka, men tidig upptäckt är helt avgörande för möjlighet till botande behandling. Cirrospatienter, vilka i många fall utgör ett förstadium med markant ökad risk att utveckla HCC (Figur 1), erbjuds därför screening med ultraljud två gånger om året för att öka chanserna till tidig upptäckt (2). Ultraljud har dock sina begränsningar då metoden är tidskrävande och beroende av operatörens skicklighet. Dessutom kan undersökningens kvalité försämras av faktorer som fetma eller tarmgas, vilka kan skymma sikten. Ultraljud har dessutom en låg sensitivitet för att upptäcka små HCC (3). Biomarkörer som ersättning för eller tillägg till ultraljud är ett alternativ, men även den kliniskt mest använda biomarkören idag, alfafetoprotein (AFP), saknar tillräcklig prestanda. Andra plasmaproteiner, liksom mikro-RNA (miRNA) vilka är små icke-kodande RNA-molekyler som deltar i posttranskriptionell genreglering (4), kan potentiellt vara nya biomarkörer.

Kurativ behandling som kan erbjudas tidigt upptäckta HCC-fall inkluderar olika kirurgiska alternativ (5). Även om levertransplantation har den bästa prognosen erbjuds många patienter, på grund av organbrist, ändå leverresektion eller lokal ablation, alternativ som är associerade med högre återfallsfrekvens (6). För närvarande finns ingen metod för att exakt förutsäga återfall efter kurativt syftande leverresektion. Biomarkörer kan spela en roll även här.

Slutligen är trombos i portvenen, sk portavenstrombos (PVT), en allvarlig komplikation till HCC. *Neutrophil extracellular traps* (NETs) (7) kan utgöra en patofysiologisk koppling mellan HCC och trombos, men denna association är inte utvärderad.

Mål

Syftet med avhandlingen är att undersöka nya potentiella biomarkörer för HCC, användbara vid screening, prognosticering eller trombosutveckling med fokus på plasma-proteiner, miRNA och NETs. Specifika mål inkluderar:

1. Att utvärdera cirkulerande plasma-proteiner som screening-biomarkörer för HCC hos patienter med cirros
2. Att utvärdera cirkulerande plasma-miRNA som screening-biomarkörer för HCC hos patienter med cirros
3. Att undersöka huruvida miRNA från HCC-vävnad kan användas för att förbättra prediktionen av HCC-recidiv efter leverresektion
4. Att analysera om nivån av NETs i plasma skiljer sig mellan patienter med HCC och patienter med cirros utan HCC

Material och metoder

Patienter till studierna inkluderades från tre olika kohorter. En öppenvårdskohort bestående av cirrospa-

tienter och patienter med nyupptäckt HCC (Kohort 1), en resektionskohort bestående av HCC som behandlas med leverresektion (Kohort 2), samt en kohort bestående av friska kontrollpersoner (Kohort 3).

I **Studie** I genomfördes en bred analys av cirkulerande plasmaproteiner för att identifiera potentiella nya biomarkörer för HCC-screening (8). Totalt inkluderades 313 patienter utvalda från Kohort 1 och Kohort 2. Proteiner analyserades i ett första steg med antingen suspension bead array (SBA) eller proximity extension assay (PEA) i en discovery kohort om 172 patienter (64 HCC och 108 cirros). Verifiering utfördes därefter på utvalda proteiner med antingen ELISA, Luminex, eller på en automatiserad elektrokemiluminescens (ECL)-plattform. Verifieringskohorten inkluderade 160 patienter (82 HCC och 78 cirros). Logistisk regression användes slutligen för att hitta den bästa kombinationen av markörer (inklusive ålder och kön) för tidig diagnostik av HCC.

I **Studie II** genomfördes analys av cirkulerande miRNA i plasma för att utvärdera deras prestanda som screening-biomarkörer för HCC (9). RNA-sekvensering (RNAseq) användes först för att hitta uppreglerade miRNA i HCC-vävnad jämfört med omgivande icke-tumorös levervävnad. Dessa uppreglerade miRNA analyserades därefter i plasma för att utvärdera vilka av dem som kunde detekteras. I det sista steget analyserades och jämfördes utvalda miRNA i plasma i en kohort om 200 patienter (inkluderade från Kohort 1 och Kohort 2) med antingen HCC (n = 101) eller cirros utan HCC (n = 99).

I **Studie III** (manuskript) analyserades vävnadsdata vad gäller miRNA-uttrycket i HCC vävnad i jämförelse med omkringliggande icke-tumorös levervävnad från Kohort 2 (n = 84). Differentiellt uttryckta miRNA användes i en logistisk regressionsmodell för att predicera risken för återfall i HCC efter kurativt syftande leverresektion.

I **Studie IV** analyserades cirkulerande markörer för NET-bildning i plasma hos patienter med HCC (n = 82), cirros utan HCC (n = 95) samt en grupp med friska kontrollpersoner (n = 50) inkluderade från Kohort 1 och Kohort 3 (10). NETs analyserades som citrullinerad histon H3-DNA (H3Cit-DNA), en mycket specifik markör för NET-bildning. H3Cit-DNA jämfördes därefter mellan friska kontroller och patienter med cirros utan HCC. Vidare undersöktes om förekomsten av HCC ökade på H3Cit-DNA nivån ytterligare.

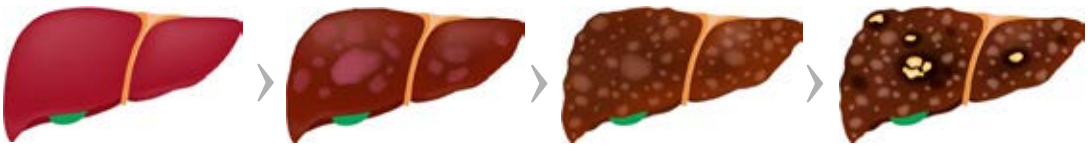
Resultat

I **Studie I** visade verifieringskohorten att fibroblast growth factor 21 (FGF21), thioredoxin reductase 1 (TXNRD1), alfa-fetoprotein (AFP) och des-gamma-karboxyprotrombin (DCP) korrelerade signifikant med HCC. Olika modeller utvärderades med logistisk regression för att finna den bästa kombinationen av dessa proteiner inklusive kliniska parametrar som ålder och kön. Den slutliga modellen visade att TXNRD1 kunde förbättra kombinationen med AFP, DCP, ålder och kön för att upptäcka HCC.

Resultat från **Studie II** visade att elva miRNA var ökade i plasma från patienter med HCC jämfört med patienter med cirros utan HCC. Två miRNA, miR-93-5p och miR-151a-3p, var signifikant korrelerade med HCC vid stegvis logistisk regression. Dock kunde inga miRNA överträffa eller förbättra kombinationen av AFP, DCP, ålder och kön som screeningmarkör för HCC.

I **Studie III** hittades tio differentiellt uttryckta miRNA i HCC-vävnad när patienter med och utan recidiv inom två år jämfördes. Dessa tio miRNA kunde förbättra en prediktiv modell för recidiv innehållandes validerade prognostiska kliniska och histologiska parametrar (AFP, tumörstorlek, mikrovaskulär invasion, satellitlesioner) i en subkohort (komplett data för n = 67). Resultaten verifierades i en kohort från The Cancer Genome Atlas (TCGA) med 161 patienter.

Studie IV visade att H3Cit-DNA var signifikant



förhöjt hos patienter med Child-Pugh B eller C jämfört med friska kontroller och patienter med Child-Pugh A. H3Cit-DNA var förhöjt hos patienter med cirros och HCC jämfört med friska kontroller, men ingen skillnad sågs mot cirrospatienter utan HCC. Vi fann heller ingen skillnad i H3Cit-DNA mellan patienter med eller utan trombos, varken historisk eller framtida trombosutveckling (medianuppföljning 22,5 månader).

Diskussion

Biomarkörer för HCC-screening är ett komplext forskningsområde där det trots stora insatser saknas biomarkörer som helt kan ersätta ultraljud. En av de mest studerade biomarkörskombinationerna idag, AFP och DCP i kombination med ålder och kön, visade sig vara bra även i våra studiekohorter. Screening av ett stort antal plasma-proteiner visade också att TXNRD1 kunde förbättra denna kombination. Vi drar slutsatsen att TXNRD1 kan fungera som en potentiell ny biomarkör för HCC-screening.

Vad gäller miRNA var resultaten blandade. Vi hittade en 10-miRNA signatur i HCC-vävnad som potentiellt kunde förbättra prediktionen av recidiv. Emellertid kunde vi inte hitta några cirkulerande miRNA i plasma som kunde förbättra resultaten vid screening av HCC hos cirrospatienter. Rollen för miRNA vid HCC behöver därför utvärderas vidare.

Vi visade slutligen att H3Cit-DNA, en NET-bildningsmarkör, var förhöjd vid avancerad cirros men utan att korrelera till HCC eller trombos. Den exakta patofysiologiska mekanismen och den kliniska relevansen behöver utvärderas vidare.

Slutsatser

Vi står fortfarande inför utmaningar när det gäller att hitta nya biomarkörer för HCC. De viktigaste fynden i denna avhandling kan summeras till:

- TXNRD1 är en potentiell ny biomarkör för HCC-screening.
- miRNA-profilen i HCC-vävnad kan potentiellt användas för prediktion av recidiv.
- Rollen för miRNA-profilen i plasma vad gäller HCC-screening behöver utvärderas vidare.
- NETs korrelerar med graden av levercirros, men inte med HCC eller trombos.

Sammantaget visar studierna på lovande resultat, men behöver valideras prospektivt i större och oberoende kohorter.

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Til manuskriptforfattere

Utfyllende forfatterinstruksjoner finnes på hjemmesiden, http://www.nfkk.org/klinisk-biokemi-i-norden/instruktioner. Litteraturhenvisninger (maksimalt 20) nummereres i den rekkefølge de angis i manuskriptteksten og skrives i Vancouver-stil, men med bare de tre første forfatterne. Dersom artikkelen har mer en tre forfattere listes de tre første etterfulgt av "et al". Forfatternes etternavn skrives først, deretter initialer (for og mellomnavn), forfatterne skilles ved komma og punktum settes etter siste forfatters initialer evt. etter "et al". Punktum brukes også etter tittel på artikkelen. Journalnavn forkortes som angitt i Pubmed, liste over forkortelser finnes i LinkOut Journals. Etter journalforkortelsen følger et mellomrom, årstall for publikasjonen, et semikolon, volum nummer, et kolon og sidetall. Overflødige sidetall fjernes, som vist i eksempelet 1989;49:483-8. Personlige meddelelser (inkludert fullt navn og årstall) og produkt informasjon skal ikke stå i referanselisten men refereres i manuskriptteksten. Dersom det er flere enn 20 referanser, må forfatteren velge ut de 20 viktigste som skal stå i bladet. De øvrige skal nummereres kronologisk i teksten, men leserne må kontakte forfatteren for å få dem.

Eksempler

Journal artikkel med inntil tre forfattere:

1. Vermeersch P, Mariën G, Bossuyt X. A case of pseudopararaproteinemia on capillary zone electrophoresis caused by geloplasma. Clin Chem 2006;52:2309-11.

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2. Fiechtner M, Ramp J, England B, et al. Affinity binding assay of glycohemoglobin by two-dimensional centrifugation referenced to hemoglobin Alc. Clin Chem 1992;38:2372–9.

Abstrakt:

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Bok kapitler:

4. Rifai N, Warnick GR. Lipids, lipoproteins, apolipoproteins, and other cardiovascular risk factors. In: Burtis CA, Ashwood ER, Bruns DE, eds. Tietz textbook of clinical chemistry and molecular diagnostics. 4th Ed. St. Louis: Elsevier Saunders 2006:903-81.

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Supplement:

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Internett kilde:

8. American Association for Clinical Chemistry. AACC continuing education. https://www.aacc.org/education-and-career/continuing-education (Tilgjengelig april 2020).

Se også NFKK's og KBN's hjemmeside: www.nfkk.org

Nordisk Forening for Klinisk Kemi (NFKK)

NFKK har som oppgave å arbeide for utviklingen av det nordisk samarbeide innen klinisk kjemi med spesiell fokus på forskning, faglig utvikling og utdanning. Den består av medlemmene i de vitenskapelige foreningene for klinisk kjemi i Danmark, Finland, Island, Norge og Sverige. Aktiviteten i NFKK foregår i like arbeidsgrupper og komiteer. Foreningen har det vitenskabelige ansvar for Scandinavian Journal of Laboratory and Clinical Investigation (SJCLI), har ansvar for utgivelse av Klinisk Biokemi i Norden, og står bak arrangering av de nordiske kongresser i klinisk kjemi.

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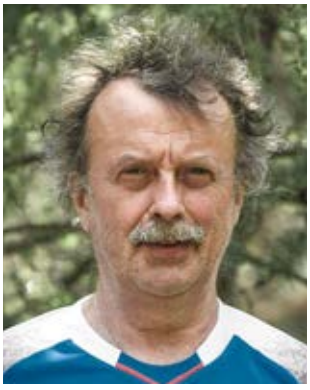

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