Host: Welcome to the ANESTHESIOLOGY journal podcast, an audio interview of study authors and editorialists.

Dr. BobbieJean Sweitzer: Hello. I’m BobbieJean Sweitzer, Professor of Anesthesiology at Northwestern University and an Associate Editor for ANESTHESIOLOGY and you are listening to an ANESTHESIOLOGY podcast designed for physicians and scientists interested in the research that appears in our journal.

Today we are speaking with two authors of publications that appear in the January 2020 issue of the journal. With us is Dr. Abraham Sonny. Dr. Sonny is the lead author of an article titled “Deficit Accumulation and Phenotype Assessments of Frailty Both Poorly Predict Duration of Hospitalization and Serious Complications after Noncardiac Surgery.”

Dr. Sonny is currently an Assistant Professor of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital in Boston, Massachusetts; however, he did this research while he was a Resident and Fellow at the Cleveland Clinic in Cleveland, Ohio. Welcome, Dr. Sonny.

Dr. Abraham Sonny: Thank you, Dr. Sweitzer. Thank you for the kind introduction. I’m thrilled to discuss this study and this forecast.

Dr. BobbieJean Sweitzer: Joining Dr. Sonny is Dr. Evan D. Kharasch who wrote an accompanying editorial “Innovation in Clinical Research Regulation.” Dr. Kharasch is Professor of Anesthesiology, Duke University School of Medicine, Durham, North Carolina and the Editor-in-Chief of ANESTHESIOLOGY. Welcome, Dr. Kharasch.

Dr. Evan Kharasch: Thank you very much and I am pleased to be with you.

Dr. BobbieJean Sweitzer: So, we’re going to start with you, Dr. Sonny. What question or questions were you trying to address with this study?

Dr. Abraham Sonny: The radius assessment tools for measuring how frail a patient is and the question with this study that we are trying to ask was among the various tools available to measure frailty, which is the best one to measure it in a surgical patient?

Dr. BobbieJean Sweitzer: So, it seems that frailty has been getting a bit of attention lately in the perioperative space. What do we already know about frailty in surgical patients?

Dr. Abraham Sonny: That is absolutely right. There’s been a lot of literature on frailty in the perioperative arena. What we know is that a good portion of our surgical patients or surgical population is frail. The prevalence of frailty in preoperative patients range from as low as 2% in some studies to as high as 40% depending on the assessment tools and population, latest population which has been studied.

We know that frailties associated with various adverse postoperative outcomes including higher mortality, higher postoperative complications and also a prolonged length of stay after surgery.

So, the two main things we know about frailty are that it does exist in a great number of our surgical patients and that it is associated with adverse outcomes.

Dr. BobbieJean Sweitzer: We mentioned you did this study, I think, when you were in Cleveland. Was this done at the Cleveland Clinic and what population of patients did you enroll?

Dr. Abraham Sonny: The study was conducted at the Cleveland Clinic main campus hospital in Cleveland, Ohio. We prospectively enrolled patients who presented to the preoperative anesthesiology clinic at the Cleveland Clinic and these patients were, of course, coming in for a preoperative evaluation before the elective noncardiac surgeries.

Dr. BobbieJean Sweitzer: And did you only target a certain age group or did you take all comers?

Dr. Abraham Sonny: The patients who presented to the preoperative clinic were a select group of patients. They were either undergoing high-risk surgeries or were ASA III or IV. So, these were a preselected group based on screening which is done over the phone or based on the kind of surgery they had.

And from all these group of patients who presented at the preoperative clinic, we selected patients who presented to two or three of our providers, preoperative screening providers who were nurses trained in these frailty assessment tools.

Dr. BobbieJean Sweitzer: So, Dr. Kharasch, in your editorial you discussed various aspects of the regulation of research involving specifically human subjects and you specifically addressed a type or a method of consent that Dr. Sonny and his colleagues used. Can you tell us a bit more about how they obtained consent and how this, perhaps, differed from a standard consent to participate in research?

Dr. Evan Kharasch: Certainly. One of the aspects of the editorial was highlighting how different research regulations can be applied in different settings but applied in a more flexible and also study-specific manner. In a great number of clinical trials, the standard form of obtaining the consent of patients to participate in research and be studied is what we call written informed consent.

And the process is where an investigator or member of the investigator’s team will describe the study to a potential subject; they will describe the process and the procedures, they’ll describe the potential risks and the potential benefits to that subject, answer any questions that the subject may have and also provide to that subject a written form which contains all that information for the subject to read and then to sign. And that’s a very common way of obtaining informed consent to participate in research.

In the study that was done by Sonny and his coworkers, they used a different process and they used what is called a waiver of written informed consent. And this was done with the approval of the hospital’s regulatory agency after that regulatory agency reviewed the protocol and the proposed method of consent.

So, the investigators provided the patients ahead of surgery with an information sheet that described the study. This was a relatively short, concise and brief document.

Then the investigator’s team obtained verbal consent to participate in the study. That consent was given preoperatively and if the subjects didn’t want to participate in the research, that was their choice and we call that an opt out.

So, informed consent was obtained, like it traditionally is, but the difference was that a long written consent form and signature of the subject was not required.

Dr. BobbieJean Sweitzer: So, who makes these rules or regulations regarding human participation in research?

Dr. Evan Kharasch: Human research regulations in the United States fall under the jurisdiction of the United States government and there are US government statutes which describe the appropriate rules, regulations, processes and procedures for doing research.

Dr. BobbieJean Sweitzer: So, Dr. Sonny, in your title you refer to deficit accumulation and phenotype assessments of frailty. Can you explain these to us and specifically how they are similar or they differ?

Dr. Evan Kharasch: Absolutely. The majority of the tools used to measure frailty can be grouped into two categories and this division is based on the underlying concept of frailty: one of which is the deficit accumulation method; and, the other one is the phenotype assessment.

The deficit accumulation concept assumes that frailty occurs due to accumulation of multiple deficits across various clinical domains. For example, a person with hypertension and diabetes is thought to be more frail than one with just hypertension. So, the more amount of comorbidities or more amount of deficits one accumulate, they’re more likely or more likely to be frail they are.
On the other hand, the phenotype model considers frailty to be a clinical syndrome which can be measured by a battery of clinical tests. There typically are thought to be five clinical features linked to this syndrome of phenotype model and these fall under the categories of weight loss, weakness, exhaustion, slowness and low physical activity level.

These can be measured by different clinical tests. For example, if you’re measuring weakness, it can be measured by the strength of your handgrip and that can be measured objectively by a handheld dynamometer.

So, this measure allows you to deliver or conduct sort of a clinical test on individuals and based on the result of these tests patients are either categorized into frail or not frail.

So, both of these concepts look at completely different aspects of frailty and come at it from different angles and both have been extensively studied in different patient populations.

Dr. Bobbie Jean Sweitzer: Yes, they seem to be quite different and just on first sort of blush it seems like my idea of what frailty is would be more determined by the phenotype assessment. But is there a standard definition of frailty?

Dr. Abraham Sonny: You’re absolutely right on that; these two tests are completely different. There are various definitions of frailty in literature, but the most broad one probably is that frailty is an increased vulnerability or a diminished capacity of an individual to cope with an external stressor.

In the perioperative context, that external stressor is the surgery and the diminished capacity is measured by these measurement tools.

Dr. Bobbie Jean Sweitzer: So, you’ve told us that you used – that there were these two different sort of general types and I think you used two very specific tools. Can you start with telling us about the Hopkins Frailty Score, which I think is the phenotype, is that correct?

Dr. Abraham Sonny: That is absolutely right. Hopkins Frailty Score is the most commonly studied phenotype-based frailty assessment tool which has been studied in the perioperative context. It, again, uses those five components of the phenotype model we just talked about. I’ll go into each component in a little bit more detail.

And the weight loss is measured as more than a 10-pound loss in the last year and the exhaustion is measured as – well, the patient felt exhausted in about three-to-four days per week in the last week or more than that.

Low physical activity, on the other hand, is measured based on patient-reported activity for the last two weeks. We use those activities and there is a certain scale called a Minnesota Leisure Scale and based on that scale, the patients can be categorized as to whether they have a good amount of activity versus low activity.

The other two measures are based on physical strength and walking speed. So, the walking speed, we allowed the patient to walk 15 feet and we measured the time taken to walk that distance and from that calculated based on a predetermined score as to whether they were – had a slow walking speed or not. And for weakness we looked at grip strength which is, again, measured by a handheld dynamometer.

These components have been validated in earlier studies to be predictive of adverse outcomes after surgery. Each component is given a score of 1 when it is present and when it is not, a score of 0 is given; and the cumulative score forms a Hopkins Frailty Score for each patient. So, this score can range from 0 to 5 and most studies have used a cutoff of 3, meaning that a score of 3 or more out of 5 is considered to be frail.

Dr. Bobbie Jean Sweitzer: I think there’s also a class of pre-frail, is that correct?

Dr. Abraham Sonny: That is right. A score of 1 or 2 is considered to be pre-frail in many studies. We did not consider that.

Dr. Bobbie Jean Sweitzer: I looked at the Minnesota Leisure Scale and I must say I was kind of amazed at how many activities they listed, but it was clear that it was probably developed in Minnesota because there was a lot of fishing and hunting activities that seemed to be included [laughter] in those measures of activities. But I assume it’s applicable across even in urban populations.

Dr. Abraham Sonny: You’re absolutely right on that and a lot of the activities our patients did did not match all the activities which are listed in the Minnesota scale. And so, for that aspect of it we worked with a physical therapist to see what is the average correlate of that in terms of amount of calories spent on doing a similar activity.

And we made correlates for the amount of calories spent which is the goal of the Minnesota Leisure Activity Scale, to measure how many calories were spent and based on which their physical activity levels measured.

So, you’re absolutely right on that. We had to go and find new scales and calories spent for new activities which are not present in the scale.

Dr. Bobbie Jean Sweitzer: Wow. It just shows again how complicated these studies can be and how much work that often goes in behind the scenes. So, just briefly maybe you can cover some of the components of the Modified Frailty Index which I believe is this cumulative deficit model.

Dr. Abraham Sonny: Certainly. The Modified Frailty Index is, again, the most commonly studied deficit accumulation frailty assessment tool in the perioperative context. It has a 11 components or variables; they just represent various comorbidities. Like we said before, history of diabetes or history of chronic obstructive pulmonary disease or a history of pneumonia in the last year or a history of congestive heart failures.

So, many of these form these 11 components and each component is given a score of 1 when present and 0 when not; and the cumulative score forms the Modified Frailty Index. A score of 4 or more out of 11 components is considered frail by most investigators and that is what we used.

Having said that, for our analysis we used the scores as a continuous variable and that is just to improve our power and our statistical power for the study, though various investigators have categorized it into frail and non-frail.

Dr. Bobbie Jean Sweitzer: So, again, I find it kind of interesting those lists of conditions because, I mean, I can kind of understand where a patient with heart failure but just a significant heart failure would be frail where just simply having diabetes doesn’t sort of naturally make you think that this is going to have a patient become frail.

Dr. Abraham Sonny: Completely agree. And this score was initially developed from a community doing an elderly score in Canada where in a large Canadian health study they looked at whether certain individuals or elderly individuals living in a community who were at high risk or mortality or falls and they had a large number of variables.

And in perioperative context, these variables were changed or as to similar variables which are more likely to be found in a perioperative patient; and those were children in that population in various studies and validated. And that is how these certain specific histories became more prominent just out of what appeared to be more significant in a perioperative context.

Dr. Bobbie Jean Sweitzer: Thank you. So, Dr. Kharasch, you mentioned how the federal government regulates research in the United States and I think in your editorial you describe what’s known as the Common Rule. Can you tell us a bit more about that and does this apply to all research conducted in the US?

Dr. Evan Kharasch: The Common Rule is a nomenclature term, if you will, for the federal research regulations and the Common Rule specifically applies to research that is either conducted by or is funded by one of the various federal agencies which govern the Common Rule.

Institutions which are conducting research that is subject to the Common Rule have to abide by it and apply the regulations. But if...
studies are not funded by the federal government or one of the agencies which subscribes to the Common Rule, then a particular institution can choose to either follow those Common Rule regulations or not follow those Common Rule regulations.

They'd still have to protect human subjects, they still have to ensure all of the rights and safety of research subjects, but they don't necessarily need to implement all of the specific rules that are enumerated.

And it gives those institutions a little bit greater flexibility in how they regulate research and how investigators implement research.

Dr. BobbieJean Sweitzer: So, I think most of us who have done any research are much more familiar with institutional review boards or commonly known as the IRB. How does the IRB, I guess, factor into all of this and what is the relationship between that and the federal government regulation?

Dr. Evan Kharasch: The IRB or institutional review board, which is perhaps a bit of a minisnorum because it's not meant to protect institutions, it's meant to protect human research participants, another term for it is a research ethics committee or an ethics board and that's a term which is sometimes used in Europe.

But that is the entity that is responsible for reviewing a research protocol, assessing the risks and benefits and for reviewing the document or informed consent document that an investigator would give to a subject and ask that subject to sign.

Now, an institutional review board can be located at the institution or the organization where the research is occurring. For example, many, many universities have their own institutional review boards, but an institutional review board can also be separate and there are a great many independent separate institutional review boards set up by various companies and various organizations around the country. And it's up to the institution where the work is being done to determine which IRB will govern that research.

And there are some rare instances in which than more than one IRB can govern a particular protocol and that's when a research protocol is sponsored by one of the federal government agencies or is conducted at one of the federal government agencies. And then there may be multiple institutional review boards which are making rules about how one particular protocol would be implemented.

Dr. BobbieJean Sweitzer: Dr. Sonny, what were the specific outcomes you looked for in your study?

Dr. Abraham Sonny: Our primary outcome was days of prolonged hospitalization or specifically the additional number of days the patient stayed in the hospital after surgery, more than what is expected for that particular surgery at Cleveland Clinic. Our secondary outcome was a composite of 30-day readmission and 30-day postoperative complications.

Dr. BobbieJean Sweitzer: So, you were trying to see whether one or either of these predicted that and how they compared to each other in predicting those outcomes?

Dr. Abraham Sonny: Correct.

Dr. BobbieJean Sweitzer: Dr. Kharasch, I think in your editorial you point out that Dr. Sonny's study can be described as a comparative effectiveness research study. Can you tell us what this means?

Dr. Evan Kharasch: Certainly. Comparative effectiveness research is a particular kind of clinical study and it has a very specific kind of definition and it refers to research that compares the benefits or the risks or harms of various kinds of interventions and strategies for preventing or diagnosing or treating various health conditions or health outcomes in what we call a real-world setting.

Many clinical trials have very strict and rigid rules to make sure that the various study populations are similar to each other, but that doesn't always reflect the great diversity of patient populations in what we call the real world.

So, comparative effectiveness research looks at a broad scope or a broad group of populations in what we might call the "real world" and also looks at various different intervention and that's very different than some clinical studies which may compare some intervention to a placebo or a nonactive kind of intervention.

Dr. BobbieJean Sweitzer: So, how does it differ from a placebo-controlled trial?

Dr. Evan Kharasch: It differs in the sense that a placebo-controlled trial—and a placebo is an inactive intervention—it could be a sugar pill or a sham procedure that is designed so that the subject in the outcomes can't be affected by a subject or an investigator knowing what was done. It's what we call blinding.

And many, many clinical trials will compare a new drug or a new intervention compared to a placebo and those kinds of trials may ask "Does this new thing work?"

Comparative effectiveness research looks at two active interventions and says, "Of these active interventions, which we currently do or currently may do, which one works better?"

Dr. BobbieJean Sweitzer: Thank you. So, Dr. Sonny, what percentage of patients did you find in your study that classified as frail?

Dr. Abraham Sonny: When frailty was measured using Hopkins Frailty Score, 18% of our cohort was frail; that's about 184 patients out of 1,042 patients we enrolled. And when we used Modified Frailty Index, about 23% of our cohort were frail.

Dr. BobbieJean Sweitzer: Was there pretty good overlap in those two groups?

Dr. Abraham Sonny: Yes. There was significant overlap between the two groups.

Dr. BobbieJean Sweitzer: So, what did you find regarding a determination of frailty in this patient population and the outcomes that you were looking at?

Dr. Abraham Sonny: We found that both scores were similarly poor at predicting both our outcomes, both the primary and our secondary outcome, which are prolonged hospitalization and the composite of postoperative complications and readmission.

Dr. BobbieJean Sweitzer: So, given what you told us at the very beginning of how the frailty has been shown to be associated with, I think, poor outcomes of various types, were you surprised by these findings?

Dr. Abraham Sonny: We were very surprised at these findings. These are completely contrary to what we were expecting. In fact, our study sort of stands in contrast to various other studies showing a significant association between frailty and adverse postoperative outcomes.

Dr. BobbieJean Sweitzer: Dr. Kharasch, you discuss the concept of minimal risk as well in your editorial. Where does this term come from and what does it mean?

Dr. Evan Kharasch: The term, again, comes from federal regulation and we're interested in the term because we often consider comparative effectiveness research to be minimal risk. Again, we're not testing something that is brand new. We're testing two relatively common approaches to a particular disease or a treatment of disease and asking which of these is better.

So, minimal risk is a term that means that the probability or the magnitude of some potential risk or harm in the research, that risk is not greater than the risk that one may encounter in daily life or during the performance of normal routine or physical or psychological examinations or tests.

Dr. BobbieJean Sweitzer: Does minimal risk factor into the requirements for a consent?
Dr. Evan Kharasch: It can. When there is minimal risk, the IRB has an option and it can use more innovative and more flexible approaches to conducting the regulatory aspects and requirements of research.

For example, if a study is minimal risk, an IRB can decide that it can be done with a waiver of written consent or in, perhaps, rare instances, a waiver of consent at all. And that’s because it is considered to be minimal risk and of little or no risk to the research subject.

And the importance of that is that it decreases the burden on researchers, it decreases the burden on potential research participants in terms of constructing and having to read a long, complicated consent form. So, it’s the aspect of flexibility to research which is the key in the concept of minimal risk.

Dr. BobbieJean Sweitzer: Dr. Sonny, you talked about C statistics or using C statistics in this study. Can you explain to our listeners what importance that had in your study?

Dr. Abraham Sonny: C statistic is a measure of predictive accuracy of a test. Predictive accuracy has two components: calibration which, of course, is a correlation or agreement between a test and an outcome; and, the second component is discrimination.

C statistic specifically measures discrimination. Discrimination refers to how well a test or a model can categorize individuals who will have an adverse outcome versus not.

The C statistic ranges from .0 to 1, a test with no discriminative ability will have a C statistic of .5 and one which will have an ability to perfectly differentiate between patients who will have an adverse outcome versus not will have a C statistic of 1.

This was very important for our study since discriminative ability is probably the most important aspect when evaluating the clinical utility of a score. For instance, the clinician would like to know if frailty measurement tool will identify a subset of patients who will do poorly after surgery and this is best measured by a C statistic.

Dr. BobbieJean Sweitzer: We’ve acknowledged that your findings were different from what other studies have suggested about the importance of frailty as a predictor of risk in surgical patients. Can you share your thoughts on why perhaps your study contrasted with previous work?

Dr. Abraham Sonny: Thank you for that question. We have evaluated in-depth and we think the difference between the findings of our study and previous literature can mostly be attributed to—our robust study design.

Various other studies evaluating frailty before having evaluated that a relationship between frailty and postoperative outcomes and reported as statistically significant odds ratio which basically looks at the calibration portion of the predictive accuracy and not discrimination and I think it overlooks the scores’ clinical utility.

We analyze prediction errors and discriminative ability of the frailty scores in predicting postoperative outcomes which is, I think, a better way of looking at the clinical utility of the score.

Dr. BobbieJean Sweitzer: Not disregarding the importance and rigor of your study, but where do you think we go from here to perhaps further elucidate what may be a bit of a conundrum regarding frailty and possible impacts on surgical outcomes?

Dr. Abraham Sonny: We think that the poor predictability of Hopkins Frailty Score and Modified Frailty Index may reflect the fact that neither was developed to actually assess surgical risk. Most of these scores, when used in the perioperative context, were initially adapted from scores which were developed to predict adverse events among elderly individuals living in the community.

So, as a next step I think we need novel frailty assessment tools which are specifically developed in a surgical cohort and as a surgical risk assessment tool and the competence of those scores might be better suited for assessing perioperative frailty.

Dr. BobbieJean Sweitzer: Dr. Kharasch, any final thoughts or comments?

Dr. Evan Kharasch: As clinical research becomes more and more important and clinical research regulations become more and more complex increasing the cost and time and duration of clinical studies, I think it’s important for us and particularly the federal government and IRBs to be aware of potential ways to increase flexibility, be more responsive and lower the cost and timeline of doing research all while we continue to protect human research participants and ensure the integrity of research.

Dr. BobbieJean Sweitzer: I hope today’s discussion will interest many of our listeners and lead you to read this important article to learn more. Thank you, Drs. Sonny and Kharasch for discussing your work with us today. I wish you well as you continue your efforts to enhance the practice of anesthesiology and strive to improve the care of our patients.

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