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Cross-sectional design with a short-term follow-up for prognostic imaging biomarkers☆

Joong-Ho Won [a], Xiao Wu [b], Sang Han Lee [c], Ying Lu [d,*]

[a] Department of Statistics, Seoul National University, Republic of Korea

[b] Department of Biostatistics, Harvard University, United States

[c] Center for Biomedical Imaging and Neuromodulation, The Nathan S. Kline Institute for Psychiatric Research, United States

[d] Departments of Biomedical Data Science, Radiology, and Health Research & Policy, Stanford University School of Medicine, United States

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ABSTRACT

Medical imaging techniques are being rapidly developed and used for diagnosis and prognostic predictions. To validate a prognostic predictive utility of a new imaging marker, a temporal association needs to be established to show an association between its baseline value with a subsequent chance of having the relevant clinical outcome. Validation of such techniques has several difficulties. First, different from techniques based on blood or tissue specimen, imaging techniques often have no historical samples to study and require new studies to collect data. For rare events, it can be costly. Second, the rapid technology evolution requires such validation studies to be short in order to keep the evaluation relevant. A new statistical design is proposed that extends traditional prospective cohort study by adding cases with known time of events and including a short-term follow-up to estimate the prospective odds ratio for the clinical endpoint of interest within a reasonably short duration of time. Under a Markov model, this new design can deliver a consistent estimate of the odds ratio and a formula for asymptotic variance. Numerical studies suggest that the new design induces a smaller variance than the corresponding prospective cohort study within three follow-ups. An application to Alzheimer's disease data demonstrates that the proposed design has a potential to be useful to rapidly establish a prognostic validity of a new imaging marker within a reasonable time, with a small sample size.

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1. Introduction

Precision medicine depends on successfully developed biomarkers to accurately predict a risk of adverse health outcomes, such as having a disease, osteoporotic fracture, heart failure, or death. A biomarker is defined as "a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to therapeutic intervention (Biomarkers Definitions Working Group, 2001)". New biomarkers are

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* Corresponding author.
E-mail address: ylu1@stanford.edu (Y. Lu).

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discovered in an accelerated pace due to recent advances in genetic, genomic, and protein-based methods of treating diseases as well as evolutions in *in vivo* imaging and tissue collection technologies (Altar, 2008). Biomarkers have multiple applications, including prediction of disease risk, detection of an existing disease, and estimation of patient prognosis (European Society of Radiology, 2010). To be useful as a prognostic tool, a biomarker has to be scientifically validated through statistical studies. As an illustration, suppose that we are interested in the clinical event of Alzheimer's disease (AD), the most common form of dementia, among those with mild cognitive impairment (MCI), a high risk group for this disease, and have a biomarker that takes a value of H or L, denoting "high" and "low" respectively. We want to see if the baseline measurement of H or L will predict the risk of AD in, say, the next year. Among various designs for scientific validation of the marker's predictive utility, prospective cohort study and (nested) case-control study are the most relevant.

Prospective cohort study (see, e.g., Porta et al., 2014) is a form of longitudinal study to evaluate a potential association of the biomarker and the event. In such a study, a group of participants from a population is selected, and each individual in the group is followed for many years to track the occurrence of the event of interest. In the example of AD above, we may measure the biomarker status for a group of elderly MCI subjects, and follow them annually to see who convert to AD. If the conversion rates turn out to be significantly different between those with the biomarker status of H and those with L, we conclude that the biomarker of question is indeed a valid prognostic biomarker for AD. A cohort study controls many confounding factors and is the most desirable approach in validating the desired association. However, it is expensive and not always feasible, especially if the event of interest is rare.

As an alternative, case-control study (see, e.g., Schlesselman, 1982) selects cases, e.g., those elderly who had a conversion from MCI to AD before the baseline of the study, and find those without a conversion with all the other known risk factors matched to those cases. We then look back their biomarker status in the past to see the association. Breslow (Breslow, 1976, 1996) showed that a case-control study can yield the same odds ratio as that would have been obtained from a prospective cohort study. The advantage of case-control study is that it can be performed at a lower cost for rare events than the corresponding prospective cohort study, and in a shorter time. The validity of a case-control study, however, depends upon its ability to evaluate the historical values of the potential biomarker. For the validation of serum- or tissue-based biomarkers, nested case-control study has been used conventionally. This design relies on historically conducted cohort studies, from which the cases and the controls are selected retrospectively. It then takes advantage of historically collected serum or tissue specimen in the cohort studies to determine the historical values of the potential biomarker.

Imaging biomarkers measure anatomical, functional or molecular parameters using radiological imaging technologies. Compared to tissue-based and serum-based biomarkers, characteristics of imaging biomarkers include non-invasiveness, spatiotemporal resolution, ability to be measured longitudinally, and adaptivity to technological advances. Due to these characteristics, imaging biomarkers are increasingly used in major medical areas such as cancer, cardiovascular diseases, musculoskeletal diseases, neurological diseases, and so on (European Society of Radiology, 2010). As for validation, longitudinal cohort study is particularly difficult for imaging biomarkers, because of the rapid pace of technological innovations in imaging sciences: often the technology becomes obsolete before the conclusion of a cohort study is made. Cost and feasibility issues for rare events still pertain. Nested case-control study design does not work for imaging biomarkers either, because many biomarkers depend on the technology that did not exist in the past, thus the historical values are impossible to evaluate. For example, in studying AD, the hippocampus as an imaging biomarker has drawn a significant attention by researchers because of the nature of neuronal loss related with memory loss in AD. As imaging technology develops, it has become feasible to observe hippocampus *in vivo* through non-invasive ways such as magnetic resonance imaging (MRI). Numerous studies have reported that hippocampus atrophy is associated with AD (Schuff et al., 2009, and references therein) and loss of hippocampal volume predicts progression to AD (Jack et al., 1999). Due to the insidious nature of AD, longitudinal study is desirable to confirm that temporal change of hippocampal volume has a prognostic potential as an MRI-based biomarker for AD; some large-scale brain MRI cohort studies were launched in more than 10 years ago, and are still on-going (Weiner et al., 2015). However, the most developed MRI scanner is not available to every participant in the study because of the rapidly developing technology. For instance, 1.5T MRI scanners were popular in a few years ago, but nowadays 3T scanners are demanded in most AD studies.

Another example is from the research of osteoporosis, where the incidence rate is low and standard diagnosis method is low-cost already. The broadband quantitative ultrasonometry (QUS) for studying bone mineral density and structure at low cost was developed before 1984 (Langton et al., 1984). However, its prognostic utility of measuring osteoporic fracture risk was not established until a longitudinal cohort study through the Study of Osteoporotic Fractures (SOF) confirmed it in 1997 (Bauer et al., 1997). Although the SOF cohort had previous visits, it was not possible to use a nested case-control study design and the past SOF data because the historical QUS measures were not available. In recent years, the costs of QUS and dual X-ray absorptiometry (DXA), a competing osteodensitometry method, have both gone down to less than $50 per scan, making future technologies much more difficult to validate their prognostic utility through prospective cohort studies.

Thus there is a strong demand for a design that is more efficient and rapid than prospective cohort designs so not to wait until all normal subjects to develop diseases, while estimating the odds ratio of a new imaging biomarker unbiasedly compared with cross-sectional designs. We propose a hybrid case-control study design with a short-term follow-up in order to estimate the odds ratio of a new (potential) biomarker consistently within a short time and with a feasible sample size. Our design takes advantage of a case-control design to enrich cases for non-fatal outcomes, and a feature of imaging biomarkers that they can be measured repeatedly for study participants via follow-ups. This design, however, can be applied to any other biomarkers as long as they share these characteristics, such as mobile biomarkers. We use statistical modeling to impute the

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