Università degli Studi di Padova

Scuola di Specializzazione in Medicina Nucleare

Corso di Statistica Medica AA 2019-20
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Study Designs and Statistical Analysis

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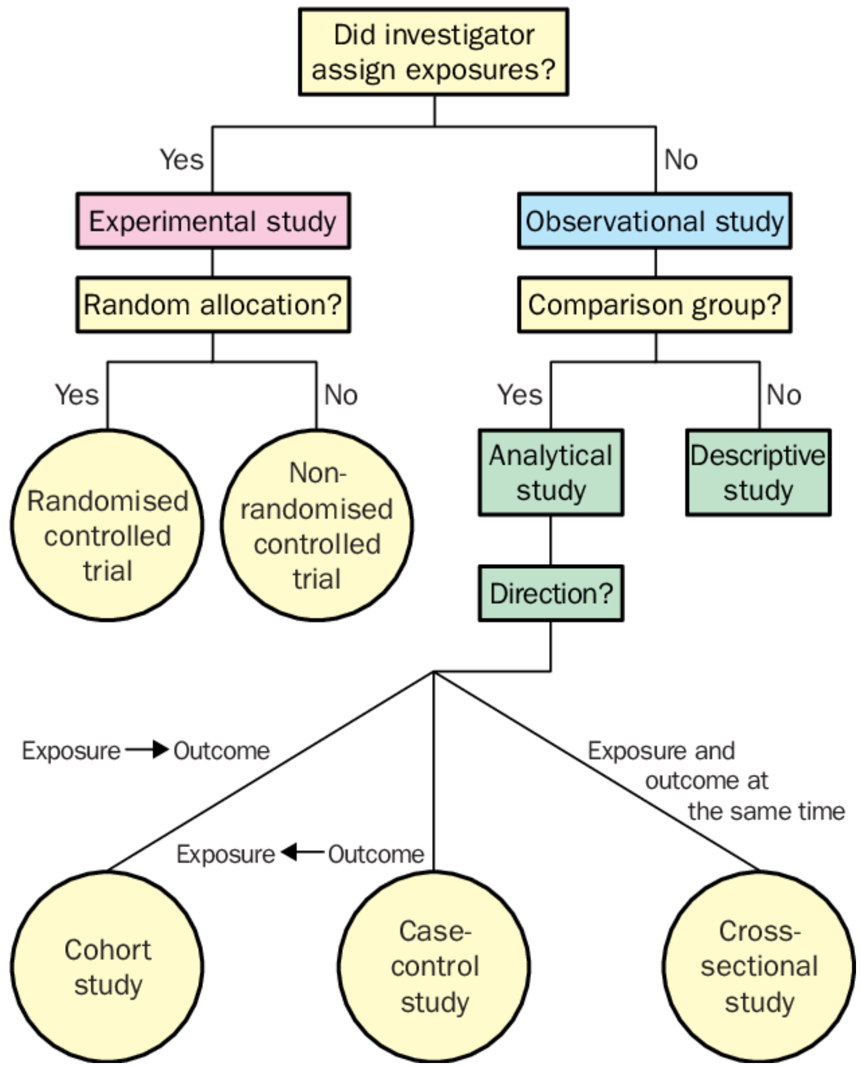
Study Designs



Schulz KF, Grimes DA. *The Lancet Handbook of Essential Concepts in Clinical Research*. Philadelphia, PA: Elsevier; 2006.

Study Designs

Table 1 Comparative effectiveness research methods

1. Methods of evidence generation
   - 1.1. Randomized clinical trials
     - Head to head trials: randomization at the subject level
     - Cluster randomized trials: randomization at group levels (eg hospitals)
     - Adaptive designs: eg Bayesian adaptive randomization
     - Pragmatic trials: control arms defined as "usual practice," broad inclusion criteria; evaluates new interventions in realistic healthcare settings
   - 1.2. Observational study designs
     - Prospective and retrospective cohort: subjects are identified by the exposure variable (eg treatment) and followed over time for the occurrence of outcome events (eg death)
     - Case−control: subjects are identified by the outcome and retrospectively evaluated for the exposure of interest
     - Cross-sectional: evaluates exposure and outcomes simultaneously at a single point or period of time; cannot distinguish whether exposure precedes the outcome
     - Ecological: studies of aggregated data (eg by country)
     - Other: registry studies, administrative health claims databases; patterns-of-care studies
2. Methods of evidence synthesis
   - 2.1. Meta-analysis: quantitative methods to synthesize evidence (eg fixed-effects)
   - 2.2. Systematic reviews: descriptive methods to synthesize evidence
   - 2.3. Mathematical models: decision analytic models (often used in cost-effectiveness analyses)

Clinical Investigation: Head and Neck Cancer

Observational Study Designs for Comparative Effectiveness Research: An Alternative Approach to Close Evidence Gaps in Head-and-Neck Cancer

Bernardo H.L. Goulart, MD,[*,‡] Scott D. Ramsey, PhD,[*,‡] and Upendra Parvathaneni, MBBS[†,‡]

*Fred Hutchinson Cancer Research Center, Division of Public Health Sciences, Hutchinson Institute for Cancer Outcomes Research (HICOR), Seattle, Washington; and †Department of Radiation Oncology, ‡University of Washington, Seattle, Washington

Received Mar 20, 2013, and in revised form May 27, 2013. Accepted for publication May 31, 2013.

Observational vs Experimental Studies

Table 2 Advantages and limitations of randomized controlled trials and observational studies

Randomized controlled trial		Observational study	
Advantages	Limitations	Advantages	Limitations
Measures treatment efficacy	Poor generalizability of results	Measures treatment effectiveness	Subject to selection bias and confounding
Lack of selection bias by virtue of randomization	Relative short follow-up time	Good generalizability of results	Methodologically complex
Well-defined study populations	Costly	Cheaper; less time-consuming	Heterogeneous patient populations
Homogeneous patient populations	Time-consuming; long timelines to conclude	Provides resource utilization and cost data	Less detailed clinical information
High patient adherence to treatment protocols	Not enough power to compare rare events	Long follow-up times; well-powered to detect rare events	Data often not collected for research purposes
Research-oriented, high-quality data collection protocols	Not enough power to study rare diseases	Large sample sizes; well-powered to study rare diseases	Variable patient adherence; does not capture new treatments
Detailed clinical information	Control groups often do not reflect current practice	Control groups reflect current practices	Quality of reporting highly variable

Clinical Investigation: Head and Neck Cancer

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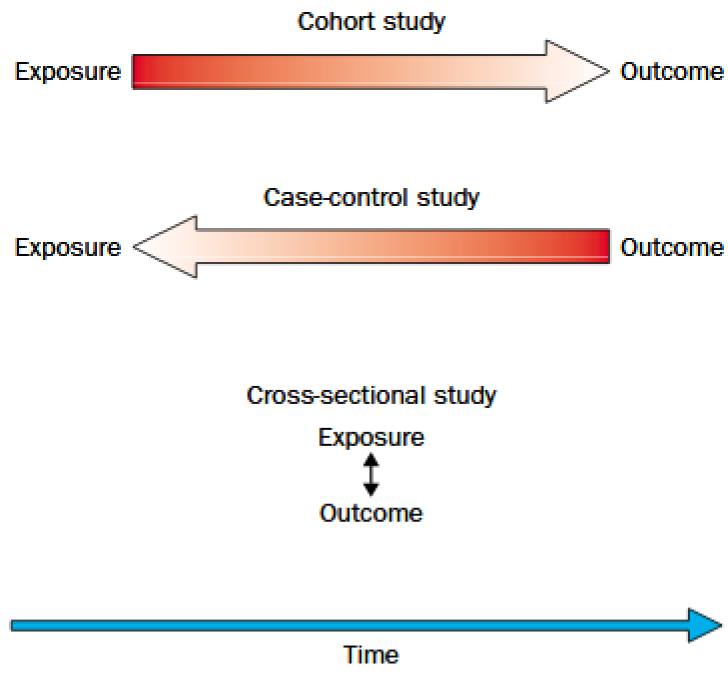
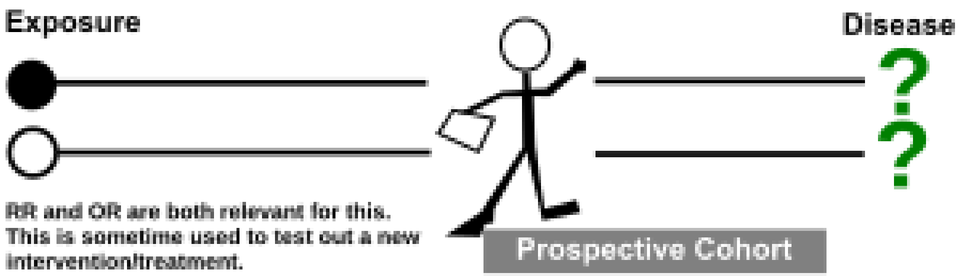
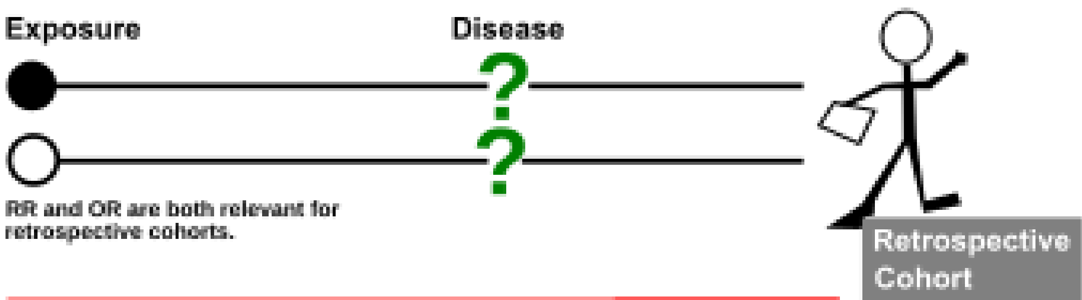
Cohort, case-control, cross-sectional studies



Cohort study





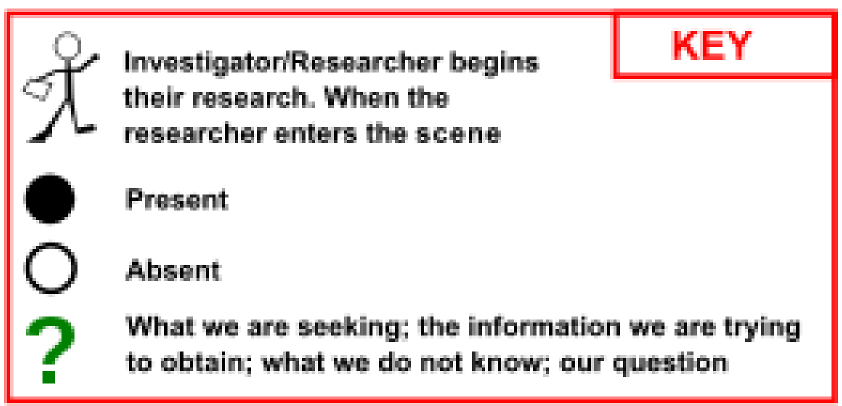
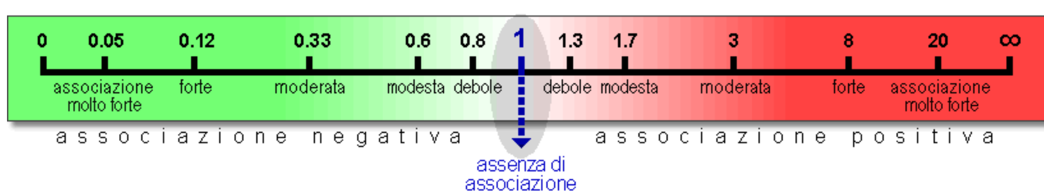


TABLE 1 Two-by-Two Table for a Cohort Study

Group	Outcome		Total
	Yes	No	
Exposed	*a*	*b*	[*a* +*b*]
Unexposed	*c*	*d*	[*c* + *d*]
Risk ratio	[*a* / (*a* + *b*)] / [*c* / (*c* + *d*)]		



Cohort study

In: C.C. Blackmore, P. Cummings. Observational Studies in Radiology. American Journal of Roentgenology. 2004;183: 1203-1208.

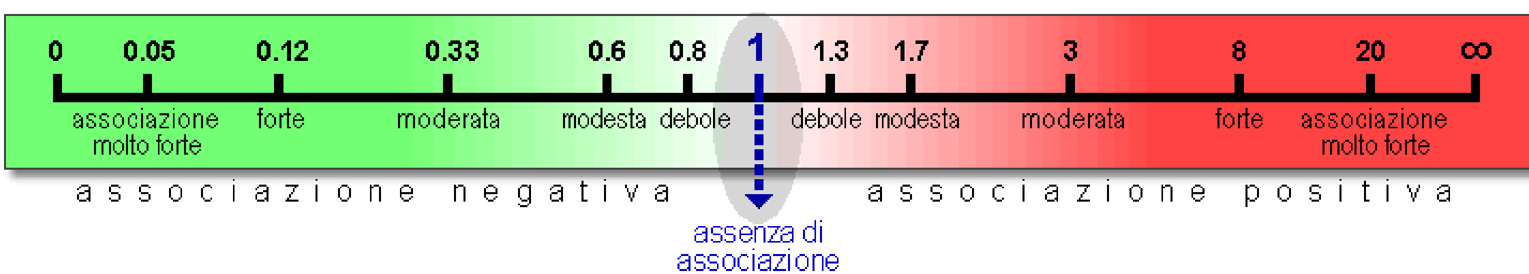
TABLE 2 Cohort Study Comparing Reaction Rates Using Low-Osmolar Versus High-Osmolar Intraarterial Contrast Media (Risk Ratio = 0.71)

Group	Reaction	No Reaction	Total
Low-osmolar	[*a*] 942	[*b*] 8,482	[*a* + *b*] 9,424
High-osmolar	[*c*] 1,601	[*d*] 9,833	[*c* + *d*] 11,434
Risk ratio			
Formula	$[a / (a + b)] / [c / (c + d)]$		
Result	(942 / 9,424) / (1,601 / 11,434) = 0.71		

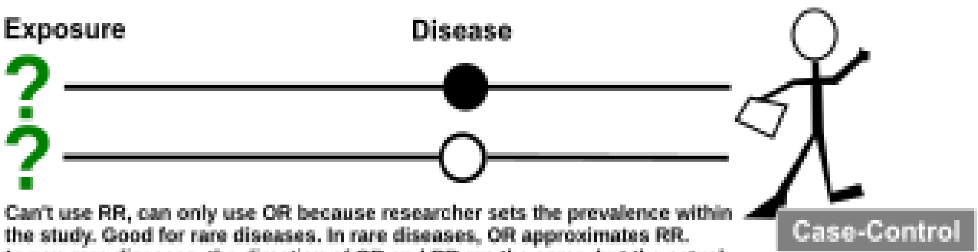
Note.—Derived from Bettmann et al. [16].

16. Bettmann MA, Heeren T, Greenfield A, Goudey C. Adverse events with radiographic contrast agents: results of the SCVIR contrast agent registry. *Radiology* 1997;203:611–620

The study by Bettmann et al. [16] compared the intraarterial use of low-osmolar contrast material with intraarterial high-osmolar contrast material in diagnostic procedures. When compared with high-osmolar contrast material, low-osmolar contrast material was associated with a lower rate of adverse events, with an unadjusted risk ratio of 0.71 (95% CI, 0.67, 0.75) (Table 2) [16].



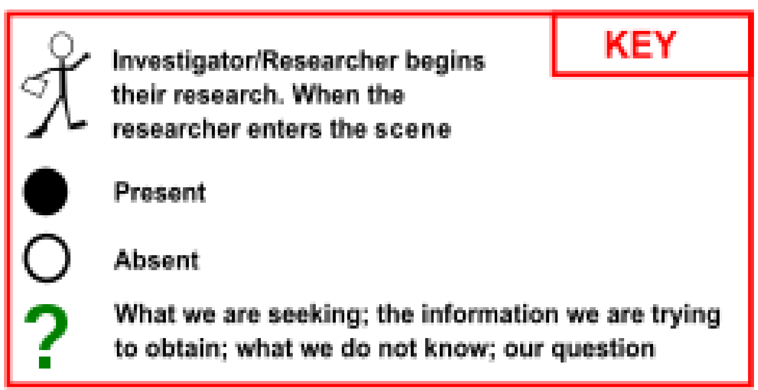
Case-control



Can't use RR, can only use OR because researcher sets the prevalence within the study. Good for rare diseases. In rare diseases, OR approximates RR.
In non-rare diseases, the direction of OR and RR are the same, but the actual number obtained of OR and RR are different. You CANNOT obtain a RR for this. It makes no sense to.

TABLE 3 Two-by-Two Table for Case-Control Study

Group	Case	Control
Exposed	*a*	*b*
Unexposed	*c*	*d*
Odds ratio	$(a / c) / (b / d) = ad / bc$	



Case-control

In: C.C. Blackmore, P. Cummings. Observational Studies in Radiology. American Journal of Roentgenology. 2004;183: 1203-1208.

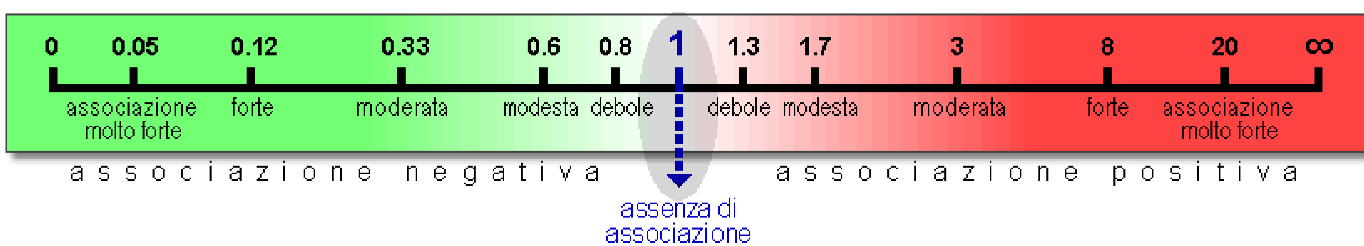
TABLE 5 **Case-Control Study of Mammography Screening and Mortality due to Breast Cancer (Odds Ratio = 0.75)**

Group	Mortality due to Breast Cancer	Alive, or Death from Other Cause
Offered screening	[*a*] 51	[*b*] 312
Not offered screening	[*c*] 147	[*d*] 678
Odds ratio		
Formula	*ad* / *bc*	
Result	(51) (678) / (312) (147) = 0.75	

Note.—Derived from Moss et al. [8].

8. Moss SM, Summerley ME, Thomas BT, Ellman R, Chamberlain JO. A case-control evaluation of the effect of breast cancer screening in the United Kingdom trial of early detection of breast cancer. *J Epidemiol Community Health* 1992;46:362–364

The odds ratio using the case-control approach for this study was approximately the same, (51) × (678) / (312) × (147), or 0.75 (95% CI, 0.52, 1.08).



Case-control vs cohort

In: C.C. Blackmore, P. Cummings. Observational Studies in Radiology. American Journal of Roentgenology. 2004;183: 1203-1208.

TABLE 4 **Cohort Study of Mammography Screening and Mortality due to Breast Cancer (Risk Ratio = 0.74)**

Group	Mortality due to Breast Cancer	Alive, or Death from Other Cause	Total
Offered screening	[*a*] 51	[*b*] 22,647	[*a* + *b*] 22,698
Not offered screening	[*c*] 147	[*d*] 48,324	[*c* + *d*] 48,471
Risk ratio			
Formula	[*a* / (*a* + *b*)] / [*c* / (*c* + *d*)]		
Result	(51 / 22,698) / (147 / 48,471) = 0.74		

Note.—Derived from Moss et al. [8].

TABLE 5 **Case-Control Study of Mammography Screening and Mortality due to Breast Cancer (Odds Ratio = 0.75)**

Group	Mortality due to Breast Cancer	Alive, or Death from Other Cause
Offered screening	[*a*] 51	[*b*] 312
Not offered screening	[*c*] 147	[*d*] 678
Odds ratio		
Formula	*ad* / *bc*	
Result	(51) (678) / (312) (147) = 0.75	

Note.—Derived from Moss et al. [8].

8. Moss SM, Summerley ME, Thomas BT, Ellman R, Chamberlain JO. A case-control evaluation of the effect of breast cancer screening in the United Kingdom trial of early detection of breast cancer. *J Epidemiol Community Health* 1992;46:362–364

The risk ratio using the cohort data was [51 / (51 + 22,647)] / [147 / (147 + 48,324)], or 0.74 (95% CI, 0.54, 1.02). The odds ratio using the case-control approach for this study was approximately the same, (51) × (678) / (312) × (147), or 0.75 (95% CI, 0.52, 1.08).

Case-control vs cohort

In: C.C. Blackmore, P. Cummings. Observational Studies in Radiology. American Journal of Roentgenology. 2004;183: 1203-1208.

TABLE 6 **Two-by-Two Table for Cohort Study When the Outcome Is Rare (Odds Ratio = 2.00, Risk Ratio = 1.98)**

Group	Outcome (Death)		Total
	Yes	No	
Exposed (test A)	[*a*] 2	[*b*] 100	[*a* + *b*] 102
Unexposed (test B)	[*c*] 10	[*d*] 1,000	[*c* + *d*] 1,010
Odds ratio			
Formula	*ad* / *bc*		
Result	(2) (1,000) / (100) (10) = 2.00		
Risk ratio			
Formula	[*a* / (*a* + *b*)] / [*c* / (*c* + *d*)]		
Result	(2 / 102) / (10 / 1,010) = 1.98		

TABLE 7 **Two-by-Two Table for Cohort Study with Very Common Outcome (Odds Ratio = 2.00, Risk Ratio = 1.09)**

Group	Outcome (Death)		Total
	Yes	No	
Exposed (test A)	[*a*] 100	[*b*] 10	[*a* + *b*] 110
Unexposed (test B)	[*c*] 1,000	[*d*] 200	[*c* + *d*] 1,200
Risk ratio			
Formula	[*a* / (*a* + *b*)] / [*c* / (*c* + *d*)]		
Result	(100 / 110) / (1,000 / 1,200) = 1.09		
Odds ratio			
Formula	*ad* / *bc*		
Result	(100) (200) / (10) (1,000) = 2.00		

Selection bias

In: C.C. Blackmore, P. Cummings. Observational Studies in Radiology. American Journal of Roentgenology. 2004;183: 1203-1208.

TABLE 8 Case-Control Study of Head Injury as a Predictor of Cervical Spine Fracture Using Emergency Department Trauma Patients as Cases and Controls (Odds Ratio = 10.0)

Group	Fracture	No Fracture
Head injury	[*a*] 52	[*b*] 13
No head injury	[*c*] 116	[*d*] 291
Odds ratio		
Formula	*ad* / *bc*	
Result	(52) (291) / (13) (116) = 10.0	

Note.—Derived from Blackmore et al. [14].

TABLE 9 Case-Control Study of Head Injury as a Predictor of Cervical Spine Fracture Using Admitted Trauma Patients as Cases and Controls (Odds Ratio = 1.4)

Group	Fracture	No Fracture
Head injury	[*a*] 52	[*b*] 11
No head injury	[*c*] 116	[*d*] 35
Odds ratio		
Formula	*ad* / *bc*	
Result	(52) (35) / (11) (116) = 1.4	

Note.—Derived from Blackmore et al. [14].

14. Blackmore CC, Emerson SS, Mann FA, Koepsell TD. Cervical spine imaging in patients with trauma: determination of fracture risk to optimize use. *Radiology* 1999;211:759–765

Confounding

In: C.C. Blackmore, P. Cummings. Observational Studies in Radiology. American Journal of Roentgenology. 2004;183: 1203-1208.

TABLE 2 **Cohort Study Comparing Reaction Rates Using Low-Osmolar Versus High-Osmolar Intraarterial Contrast Media (Risk Ratio = 0.71)**

Group	Reaction	No Reaction	Total
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Formula	[*a* / (*a* + *b*)] / [*c* / (*c* + *d*)]		
Result	(942 / 9,424) / (1,601 / 11,434) = 0.71		

Note.—Derived from Bettmann et al. [16].

16. Bettmann MA, Heeren T, Greenfield A, Goudey C. Adverse events with radiographic contrast agents: results of the SCVIR contrast agent registry. *Radiology* 1997;203:611–620

For example, in the study of contrast agents by Bettmann et al. [16], subjects with a history of reaction to contrast material were more likely to receive low-osmolar contrast material than were subjects without a history of contrast reaction. Furthermore, those with a history of contrast reaction were more likely to have a new adverse reaction than were those without a history of reaction. Therefore, the group that received low-osmolar contrast material included more persons with a propensity to have a reaction than did the high-osmolar contrast group. Failure to account for history of reaction would bias the risk ratio estimate for adverse outcomes. Thus, a history of contrast reactions confounded the relationship between the type of contrast material and the outcome [16].

Confounding

How to prevent counfounding *bias*:

- to restrict the study to subjects with only one level of the potential confounder;
- to stratify the subject on the basis of the confounder, to estimate within each stratum and combine the results across strata (feasible only with few strata);
- to adjust with regression methods;
- matching.

Confounding

In the results reported for the study by Bettmann et al. [16], adjustment was made for potentially confounding variables in a regression model. The results showed that low-osmolar contrast material was associated with fewer reactions than high-osmolar contrast material was, after accounting for the effects of previous contrast reaction, asthma, steroid pretreatment, race, sex, and other potential confounders [16].

NOT IT’S YOUR TURN!

European Journal of Nuclear Medicine and Molecular Imaging (2021) 48:3187–3197
https://doi.org/10.1007/s00259-021-05294-3

ORIGINAL ARTICLE

Long COVID hallmarks on [18F]FDG-PET/CT: a case-control study

Martina Sollini[1,2] · Silvia Morbelli[3,4] · Michele Ciccarelli[1] · Maurizio Cecconi[1,2] · Alessio Aghemo[1,2] · Paola Morelli[1,2] · Silvia Chiola[1,2] · Fabrizia Gelardi[1,2] · Arturo Chiti[1,2]

Received: 9 January 2021 / Accepted: 1 March 2021 / Published online: 7 March 2021

Abstract

Purpose The present study hypothesised that whole-body [18F]FDG-PET/CT might provide insight into the pathophysiology of long COVID.

Methods We prospectively enrolled 13 adult long COVID patients who complained for at least one persistent symptom for >30 days after infection recovery. A group of 26 melanoma patients with negative PET/CT matched for sex/age was used as controls (2:1 control to case ratio). Qualitative and semi-quantitative analysis of whole-body images was performed. Fisher exact and Mann-Whitney tests were applied to test differences between the two groups. Voxel-based analysis was performed to compare brain metabolism in cases and controls. Cases were further grouped according to prevalent symptoms and analysed accordingly.

Results In 4/13 long COVID patients, CT images showed lung abnormalities presenting mild [18F]FDG uptake. Many healthy organs/parenchyma SUVs and SUV ratios significantly differed between the two groups ($p \leq 0.05$). Long COVID patients exhibited brain hypometabolism in the right parahippocampal gyrus and thalamus (uncorrected $p < 0.001$ at voxel level). Specific area(s) of hypometabolism characterised patients with persistent anosmia/ageusia, fatigue, and vascular uptake (uncorrected $p < 0.005$ at voxel level).

Conclusion [18F]FDG PET/CT acknowledged the multi-organ nature of long COVID, supporting the hypothesis of underlying systemic inflammation. Whole-body images showed increased [18F]FDG uptake in several “target” and “non-target” tissues. We found a typical pattern of brain hypometabolism associated with persistent complaints at the PET time, suggesting a different temporal sequence for brain and whole-body inflammatory changes. This evidence underlined the potential value of whole-body [18F]FDG PET in disclosing the pathophysiology of long COVID.

Keywords SARS-CoV-2 · [18F]FDG PET/CT · Infection · Inflammation · Long COVID · Brain hypometabolism · Chronic COVID syndrome

European Journal of Nuclear Medicine and Molecular Imaging (2020) 47:2407–2416
https://doi.org/10.1007/s00259-020-04683-4

ORIGINAL ARTICLE

Check for updates

High-resolution PET imaging reveals subtle impairment of the serotonin transporter in an early non-depressed Parkinson's disease cohort

Patrik Fazio [1,2] · Daniel Ferreira [3] · Per Svenningsson [2,4] · Christer Halldin [1] · Lars Farde [1] · Eric Westman [3,5] · Andrea Varrone [1]

Received: 25 September 2019 / Accepted: 3 January 2020 / Published online: 4 February 2020

Abstract

Purpose The serotonin transporter (SERT) is a biochemical marker for monoaminergic signaling in brain and has been suggested to be involved inthe pathophysiology of Parkinson's disease (PD). The aim of this PET study was to examine SERT availability in relevant brain regions in early stages ofnon-depressed PD patients.

Methods In a cross-sectional study, 18 PD patients (13 M/5F, 64 ± 7 years, range 46–74 years, disease duration 2.9 ± 2.6 years; UPDRS motor 21.9 ± 5.2) and 20 age- and gender-matched healthy control (HC) subjects (15 M/5F, 61 ± 7 years, range 50–72 years) were included. In a subsequent longitudinal phase, ten of the PD patients (7 M/3F, UPDRS motor 20.6 ± 6.9) underwent a second PET measurement after 18–24 months. After a 3-T MRI acquisition, baseline PET measurements were performed with [^{11}C]MADAM using a high-resolution research tomograph. The non-displaceablebinding potential (BP_{ND}) was chosen as the outcome measure and was estimated at voxel level on wavelet-aided parametric images, by using the Logan graphical analysis and the cerebellum as reference region. A molecular template was generated to visualize and define different subdivisions of the raphe nuclei in the brainstem. Subortical and cortical regions of interest were segmented using FreeSurfer. Univariate analyses and multivariate network analyses were performed on the PET data.

Results The univariate region-based analysis showed no differences in SERT levels when the PD patients were compared with the HC neither at baseline or after 2 years of follow-up. The multivariate network analysis also showed no differences at baseline. However, prominent changes in integration and segregation measures were observed at follow-up, indicating a disconnection of the cortical and subcortical regions from the three nuclei of the raphe.

Conclusion We conclude that the serotoninergic system in PD patients seems to become involved with a network dysregulation as the disease progresses, suggesting a disturbed serotonergic signaling from raphe nuclei to target subcortical and cortical regions.

Keywords Parkinson's disease · The serotoninergic system · Raphe nuclei · Functional connectivity/graph analysis

European Journal of Nuclear Medicine and Molecular Imaging (2018) 45:720–726
https://doi.org/10.1007/s00259-017-3880-4

ORIGINAL ARTICLE

CrossMark

Preoperative prediction of microvascular invasion of hepatocellular carcinoma using ^{18}F-FDG PET/CT: a multicenter retrospective cohort study

Seung Hyup Hyun[1] · Jae Seon Eo[2] · Bong-Il Song[3] · Jeong Won Lee[4] · Sae Jung Na[5] · Il Ki Hong[6] · Jin Kyoung Oh[7] · Yong An Chung[7] · Tae-Sung Kim[8] · Mijin Yun[9]

Received: 16 August 2017 / Accepted: 6 November 2017 / Published online: 22 November 2017

Abstract

Purpose The aim of this study was to assess the potential of tumor $_{18}$F-fluorodeoxyglucose (FDG) avidity as a preoperative imaging biomarker for the prediction of microvascular invasion (MVI) of hepatocellular carcinoma (HCC).

Methods One hundred and fifty-eight patients diagnosed with Barcelona Clinic Liver Cancer stages 0 or A HCC (median age, 57 years; interquartile range, 50–64 years) who underwent $_{18}$F-FDG positron emission tomography with computed tomography (PET/CT) before curative surgery at seven university hospitals were included. Tumor FDG avidity was measured by tumor-to-normal liver standardized uptake value ratio (TLR) of the primary tumor on FDG PET/CT imaging. Logistic regression analysis was performed to identify significant parameters associated with MVI. The predictive performance of TLR and other clinical variables was assessed using receiver operating characteristic (ROC) curve analysis.

Results MVI was present in 76 of 158 patients with HCCs (48.1%). Multivariable logistic regression analysis revealed that TLR, serum alpha-fetoprotein (AFP) level, and tumor size were significantly associated with the presence of MVI ($P < 0.001$). Multinodularity was not significantly associated with MVI ($P = 0.563$). The area under the ROC curve (AUC) for predicting the presence of MVI was best with TLR (AUC = 0.704), followed by tumor size (AUC = 0.685) and AFP (AUC = 0.670). We were able to build an improved prediction model combining TLR, tumor size, and AFP by using multivariable logistic regression modeling (AUC = 0.756).

Conclusions Tumor FDG avidity measured by TLR on FDG PET/CT is a preoperative imaging biomarker for the prediction of MVI in patients with HCC.

Seung Hyup Hyun and Jae Seon Eo contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00259-017-3880-4) contains supplementary material, which is available to authorized users.