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A systematic review of the overlap of fluid biomarkers in delirium and advanced cancer-related syndromes.

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Abstract

Background
Delirium is a serious and distressing neurocognitive disorder of physiological aetiology that is common in advanced cancer. Understanding of delirium pathophysiology is largely hypothetical, with some evidence for involvement of inflammatory systems, neurotransmitter alterations and glucose metabolism. To date, there has been limited empirical consideration of the distinction between delirium pathophysiology and that of the underlying disease, for example, cancer where these mechanisms are also common in advanced cancer syndromes such as pain and fatigue. This systematic review explores biomarker overlap in delirium, specific advanced cancer-related syndromes and prediction of cancer prognosis.

Methods
A systematic literature search was conducted, using MEDLINE, PubMed, Embase, CINAHL, CENTRAL and Web of Science, to identify body fluid biomarkers in delirium, cancer prognosis and advanced cancer-related syndromes of interest. Studies were excluded if they reported delirium tremens only; did not measure delirium using a validated tool; the sample had less than 75% of participants with advanced cancer; measured tissue, genetic or animal biomarkers, or were conducted post-mortem. Articles were screened for inclusion independently by two authors, and data extraction and an in-depth quality assessment conducted by one author, and checked by two others.

Results
The 151 included studies were conducted in diverse settings in 32 countries between 1985 and 2017, involving 28130 participants with a mean age of 69.3 years. Seventy-one studies investigated delirium biomarkers, and 80 studies investigated biomarkers of an advanced cancer-related syndrome or cancer prognosis. Overall, 41 biomarkers were studied in relation to both delirium and either an advanced cancer-related syndrome or prognosis; and of these, 24 biomarkers were positively associated with either delirium or advanced cancer syndromes/prognosis in at least one study. The quality assessment showed large inconsistency in reporting.

Conclusion
There is considerable overlap in the biomarkers in delirium and advanced cancer-related syndromes. Improving the design of delirium biomarker studies and considering appropriate comparator/controls will help to better understanding the discrete pathophysiology of delirium in the context of co-existing illness.

Background

Delirium is a very common cause of acute cognitive change in people with advanced cancer (1) and is associated with increased morbidity and mortality (2, 3). Delirium is a serious and complex neurocognitive disorder characterized by acute deterioration in attention, awareness and cognition, variously affecting memory, language and visuospatial ability, orientation and perception (4).

Delirium occurs in people who are medically unwell, due to the underlying disease which has put them at risk (e.g. dementia, cancer, infection, renal impairment) or intercurrent problems, and the subsequent medical treatment (e.g. surgery, medication). Delirium can occur for any person, with those who are older, have advanced illness, and/or prior cognitive impairment most at risk (5). The prevalence of delirium in patients with advanced cancer in oncology and palliative care settings is higher than that in most other settings, including geriatrics (1, 6-9). A systematic review of palliative care patients (with 98.9% of participants with advanced cancer), reported delirium incidence rates between 3% and 45%. Delirium prevalence ranged from 13.3% to 42.3% at admission to hospital, and 25% to 62% during admission. Delirium prevalence increased up to 88% in the hours to days before death (1).

The pathophysiology of delirium is poorly understood, and largely hypothetical. Current hypotheses include: neuronal ageing, neuroinflammation, oxidative stress, neuroendocrine dysregulation, disruption to the circadian rhythm, and neurotransmitter dysregulation (10, 11). A reduction in glucose metabolism seen in people with delirium is a model with developing evidence (12, 13). Collectively, the biological correlates of delirium are referred to as ‘delirium biomarkers’. A biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease (14). Biomarkers are most commonly studied to investigate their correlation with a disease in order to better understand its underlying
pathophysiology, and subsequently inform prevention and treatment strategies for that disease. A challenge for the field of delirium research is that correlation may exist between biomarkers of delirium and those of the patient’s disease or injury which placed them at increased risk of delirium, or which precipitated it (for example sepsis or hip fracture). Such correlation should be factored into delirium biomarker research, yet rarely has been. Better understanding of the interplay between delirium pathophysiology and that of correlated conditions and diseases, for example, cancer (the focus of this review), is crucial to develop more effective prevention and treatment of delirium.

We therefore conducted a systematic review of the literature to explore the overlap between biomarkers that have been studied in delirium and biomarkers that have been studied in cancer-related syndromes. Our aim was to identify biomarkers associated with delirium and with specific clinical situations in advanced cancer (namely prognosis; cognitive impairment, anorexia cachexia, cancer pain, cancer-related fatigue, and sickness behavior); and to evaluate the nature and extent of overlap of the findings.

**Methods**

A systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (15) was conducted. In July 2017, two separate searches were conducted in MEDLINE, PubMed, Embase, CINAHL, CENTRAL, and Web of Science. The first was for literature of delirium biomarkers; the second was for literature of biomarkers in advanced cancer-related syndromes. Primary terms for the delirium search were: ‘delirium’ and ‘biomarker’. Search terms for the cancer search were: ‘cancer’, ‘neoplasms’, ‘metastasis’, ‘fatigue’, ‘sickness behavior’, ‘cancer pain’, ‘cachexia’, and ‘prognosis’. Additional terms which encompassed commonly researched biomarkers were also included. Filters in Medline were: 1: Humans; 2. English language and 3. Published from 1980 onward (when delirium was first included in the DSM, Third Edition (DSM-III)).

Search terms and filters were tailored to each subsequent database, as required. The full search strategy is provided in supplementary file 1. Reference lists of included studies and relevant systematic reviews and meta-analyses identified in the search were examined for additional eligible studies.
We included English language studies published in peer-reviewed journals that reported body fluid biomarkers in adult participants with delirium, cancer prognosis or an advanced cancer-related syndrome of interest. Studies were excluded if they reported delirium tremens only; did not measure delirium using a validated tool; the sample had less than 75% of participants with advanced cancer; measured tissue, genetic or animal biomarkers, or were conducted post-mortem. Protocols and ongoing studies were also excluded. Based on the expert knowledge of the authors in both delirium and cancer, the advanced cancer-related syndromes and prognosis were chosen based on the potential biological plausibility that the pathophysiological mechanisms could overlap with that of delirium. We limited the search to advanced cancer as this is the cancer population with the highest prevalence of both delirium and the cancer-related syndromes of interest.

The following definitions were used in this review:

**Anorexia cachexia:** A complex metabolic syndrome of involuntary weight loss associated with cancer and some other palliative conditions (16).

**Cancer related fatigue:** A distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning (17).

**Cancer-related pain:** An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (18).

**Cancer-related cognitive impairment:** Cognitive impairment that is commonly experienced by cancer patients and those in remission. The cognitive domains most commonly affected are memory, concentration, information processing speed and executive function (19).

**Sickness behaviour:** The coordinated set of behavioural changes that develop in sick individuals during the course of an infection. Sickness behavior is also seen in other illness including cancer (20, 21).

**Cancer prognosis:** The likely outcome or course of the disease; the chance of recovery or recurrence. Cancer prognosis is assessed by cancer-specific survival, overall survival, progression free survival or relative survival (22).
Search results were imported into Endnote X7 software, duplicates removed and then exported into Covidence™ (www.covidence.org). Two reviewers per search (IAD and AH: delirium search, IAD and MA: cancer search) independently applied eligibility criteria for both searches and examined title and abstracts. Exclusions were documented only for articles that required full-text to make a formal decision. Inter-reviewer disagreement on included studies was discussed to resolve any discrepancies, with the third reviewer consulted when required. Data extraction was conducted by one reviewer (IAD) using Excel (2016) with two other reviewers (MA and AH) providing input and oversight. Data extraction was guided by the REporting recommendations for tumor MARKer prognostic studies (REMARK) checklist (23).

In the absence of a gold standard risk of bias assessment for biomarker studies, one reviewer (IAD) applied an adaptation of the REMARK checklist (23) to assess the methodological quality of the included studies, with 10% verification by two other reviewers (MA and AH).

The heterogeneity of data precluded performing a meta-analysis; we therefore reported the data using a narrative synthesis approach with text and tabular summaries. The synthesis was structured according to the overlap of the biomarkers in delirium, cancer prognosis and the cancer syndromes, the biomarker type, assay used, and numbers and proportions of participants who had delirium and advanced cancer. We defined ‘overlap’ as any biomarker that was studied in both a delirium study and an advanced cancer syndrome study.

Results
The delirium search yielded 3342 articles and the cancer syndromes search 4081, giving a total of 7423 articles. An additional 25 articles were found through the hand search. After removal of 1817 duplicates and 5120 articles through title and abstract screening, we reviewed 511 full text papers and subsequently excluded 288. After initial analysis, a further 72 were excluded as they did not report a biomarker studied in delirium and advanced cancer. This resulted in a total of 151 articles included in this review: 71 reported biomarkers studied in delirium, and 80 reported biomarkers studied in a cancer syndrome or prognosis (Figure 1).

The 151 studies were conducted between 1985 and 2017 in Europe (n=86), Asia (n=33), The
Americas (n=27), Australia (n=2), and multiple regions (n=3). Studies were set in a large range of settings, with the most common in general hospital settings (n=111; 73%). Thirty-nine studies (26%) did not report the setting. Sample sizes ranged from 7-2456, with relatively even numbers of male and female participants (55.4% male). Ninety nine articles reported a mean age, with an overall weighted mean age of 69.3 years. Of the 37 articles that reported the median age of participants, the overall median age was 54.5 years. The overall age of participants in the remaining 15 articles was not possible to determine (Supplementary file 2 and 3). Blood biomarkers were examined in 138 studies, 4 studies examined biomarkers in cerebrospinal fluid (CSF), 3 in urine, and 16 (11%) did not report the type of biological material. Of the studies that reported the assay technique, diverse assays were used (n=20), with Enzyme-linked immunosorbent assay (ELISA) being the most common (n=62; 58%). Forty-four studies (29%) did not report the specific assay used. Of these, 21 studies (48%) were routinely measured biomarkers (Tables 1 and 2).

A total of 41 biomarkers were found to be common in both delirium and advanced cancer syndrome studies. The five most commonly studied biomarkers were C-reactive protein (CRP) (n=79), interleukin (IL)-6 (n=58), tumor necrosis factor alpha (TNF-α) (n=42) IL-10 (n=21) and IL-8 (n=24). Of these, 24 biomarkers had a positive association with delirium, cancer prognosis or a cancer syndrome in at least one study. No cancer studies reported having any participants with delirium, and of the delirium studies, six reported participants with cancer. Figure 2 illustrates two main populations identified from this systematic review, with the centre showing the ‘true overlap’ defined as studies that included participants with both delirium and cancer (n=6 studies).

In two of these studies, all participants in the study had cancer; in another, 64.2% of participants had cancer; in the remaining three studies, less than 30% of all participants had cancer. In three of the studies, 100% of participants who had delirium also had cancer, in another two, 26% and 27% of the delirium cohorts had cancer, and in the remaining study 14% of the delirium participants had cancer (Table 1). Although only six delirium studies reported co-existing cancer, there is still uncertainty as to how many participants in both groups of studies had both delirium and cancer. The two most common biomarkers in these six studies that reported a positive association with delirium were CRP
It is unclear however whether these biomarkers were predominantly associated with delirium or the cancer, as three of the six studies grouped the delirium participants together, irrespective of their cancer comorbidity.

The quality assessment showed a large variability in the reporting of included studies. 150 (99%) studies had a clear aim statement which included their outcome of interest. One study did not report a clear aims statement (24). One hundred and nineteen studies (79%) did not explicitly state the hypothesis; however, in most (n=94; 62%) the hypothesis could be interpreted by the study aim. All 151 studies stated the participant population in detail. No study reported all elements of the assay methods in the REMARK checklist (23). One hundred and thirty one studies (87%) did not report whether assays were blinded to the study endpoint, however 59 (45%) of those studies were objective assessments. Further, 14 studies (9%) reported a power calculation to justify their sample size. Most (n=125; 83%) of studies defined all clinical endpoints examined. Ninety seven (64%) studies undertook multivariate analysis, and of these 67 (69%) described the multivariate model and the covariates included in the model, and 23 (23%) explained the rationale for inclusion of the covariates in the models. (Supplementary file 4 and 5). Furthermore, 27 delirium studies (38%) did not report the reason for admission. Of the 44 studies that did report the reason for admission, these were predominantly for surgery- elective and acute (n=40). Most studies in the non-surgical population did not report a reason for admission, with the exception of 4 studies where the medical condition of interest occurred on admission (e.g stroke).

The methodological quality of the assay procedures only is depicted in Figure 3, with reporting of type of biological material mostly provided but much lower frequency of reporting for other critical descriptors.

**Discussion**

This is the first systematic review to our knowledge, to demonstrate the high degree of overlap in biomarkers in delirium, cancer prognosis and advanced cancer syndromes. This systematic review of 151 studies found that 41 biomarkers were independently investigated in studies of both delirium and prognosis/advanced cancer syndromes; with over half having a positive association in at least one
Biomarkers fall into three categories (though not mutually exclusive); those which present before disease onset that can help identify individuals who are most at risk of a particular disease (for example, genetic markers), those which are disease markers and as such, increase during disease progression and decrease after resolution, and thirdly, biomarker as an end-product of a disease for which levels are proportionate to ‘damage’ due to the disease (25). The findings of this systematic review suggest that categorization along these lines is less understood in delirium. For example, there is evidence to show that conditions such as sepsis and hip fracture cause changes in inflammatory markers (26, 27), however, there is little evidence about whether delirium self-propagates. Some animal model data in delirium suggests that there might be a direct impact of inflammatory markers on brain dysfunction (28). To our knowledge there was no published relationship between tumor markers and neurological brain dysfunction. Although clinical evidence suggests long term impacts on brain function, the exact pathophysiological mechanisms are poorly understood, and biomarkers to measure this are also unclear.

The issue of biomarker overlap between associated conditions has been researched in women with pre-eclampsia and polycystic ovary syndrome (29), however the overlap with respect to delirium and its associated conditions has not been well addressed. Of the 71 delirium studies, only five studies sought to determine the association with the participants’ common primary condition in their analysis. Tomasi et al. (2017) found that biomarkers differed between patients in the three groups in those with sepsis alone and those who developed sepsis-associated encephalopathy, or delirium, suggesting different mechanisms of sepsis-associated encephalopathy, delirium in people with sepsis, and sepsis itself. Likewise, Pfister et al. (2008) found differences in CRP, s100 calcium binding protein B (s100B) and cortisol in patients with sepsis-associated delirium, compared to non-sepsis associated delirium. In two studies, delirium in stroke was examined (30, 31) but these studies did not identify differences in cortisol (30) or TNF-α, IL-1β, IL-18, Brain-derived neurotrophic factor (BDNF) and Neuron specific enolase (NSE) (31) between patients who developed delirium after stroke compared to those who did not develop delirium. Moreover, Sun et al. (2016) attempted to explore the overlap of biomarkers in...
delirium and dementia in patients with cancer, however, no multivariate analysis was undertaken, therefore results of this study are inconclusive.

Although the aim of this systematic review was to explore the overlap of biomarkers in delirium and advanced cancer syndromes, the findings highlighted a bigger problem in the methodology of delirium biomarker research. The quality assessment in this systematic review found that many of the included studies were of poor methodological quality, inadequately reported, or were influenced by potential confounding factors. A potential barrier to the complete understanding of delirium pathophysiology is the lack of guidelines for conducting and reporting delirium biomarker studies. Results from this review indicate that the absence of such guidelines has likely impeded the quality of individual studies and the overall quality of this critical field of delirium research. Reporting guidelines for delirium biomarker research are an essential step to improving methodological and reporting rigor, and will increase the potential for synthesis of future studies through meta-analyses.

Several studies have previously been performed to determine biomarkers associated with delirium, however potential confounding factors could be the underlying precipitants of delirium; ie risk factors (sepsis), or underlying conditions present (for example cancer or dementia). The top five most commonly studies biomarkers in this review were inflammatory biomarkers, namely, CRP, IL-6, TNF-α, IL-10 and IL-8. The challenge with inflammatory markers is that they are non-specific and the inflammatory pathways are similar to those implicated in other conditions such as sepsis and depression (32, 33). Likewise, of the six delirium studies where there was concomitant cancer, it is very difficult to determine whether those biomarkers found were related to the cancer or the delirium itself, considering alterations in inflammatory pathways are implicated in both. Therefore, future delirium biomarker studies need to be prospectively evaluated and take into account and assess robustly other active co-morbidities such as cancer that could plausibly impact on the pathophysiological and/or biological findings. Similarly, future cancer biomarker studies must also take into account how delirium may clinically or biologically confound biomarker studies in cancer, considering the high prevalence of delirium in this population. Of the six delirium studies with cancer, three did not report the type of cancer, and of the remaining three studies, none were primary brain
tumours or brain metastases. Understanding the spread of brain cancer is important in delirium studies, and is an important consideration for future delirium biomarker studies.

Majority of the studies in this review (n=98; 65%) undertook a multivariate analysis, taking into account confounding variables. Where studies only undertook univariate analysis, it is uncertain whether any observed changes in biomarkers were related to the delirium itself, or whether these changes may have been lost when adjusted for confounding factors (such as prior cognitive impairment) in a multivariate analysis. Furthermore, there is likely to be a higher proportion of participants with both delirium and cancer in both groups of studies for which this clinical information was not assessed or that were not reported. Key methodological issues which need to be addressed in future delirium studies include adjusting for confounders such as age, gender, concurrent medication, comorbidities, prior cognitive impairment, frailty and other neurological conditions. These clinical covariates must also be clearly defined and justified. Assay procedures ought to be reported in detail, including a detailed protocol of the reagents/kits used, repeatability assessments, methods of preservation and storage, assay validity, sensitivity limits of the assay and a scoring and reporting protocol. The timing of the assay is crucial in delirium studies, and the fluctuating pathophysiological processes occurring during delirium, after delirium resolution, and in those who have not yet developed delirium, must be taken into consideration, and be separated in future studies. More standardised and detailed methods of delirium biomarker studies is a crucial step in carrying out future subgroup analyses within this cohort and improving the overall understanding of delirium pathophysiology.

Limitations are that only English language and published studies were included. It is possible that articles were missed; however, two reviewers independently screened all citations derived from a search of six relevant and diverse databases, and all reference lists of included articles were also searched. Another limitation of our study is the lack of a risk of bias tool for biomarker studies, therefore we used an adaptation of tumor marker reporting guidelines, the REMARK checklist (23). Lastly, the heterogeneity of the data precluded the conduct of a meta-analysis, and precluded any firm conclusions about the biomarkers in delirium and cancer, thus, limiting the rigor of this review.
Strengths of this review however, were that we undertook a systematic approach adhering to the PRISMA (15) and an extensive quality assessment of the included studies was undertaken.

Conclusions
This review found that there is large overlap in the biomarkers in delirium and in advanced cancer-related syndromes, although because of the heterogeneity of the studies firm conclusions about the true overlap of delirium and advanced cancer syndrome biomarkers was not possible. More robust conduct and reporting of delirium biomarker studies will help to better understand the pathophysiology of delirium in the context of co-existing pathophysiology. An improved understanding of the clinical and biological associations of delirium and advanced cancer syndromes in future prospective studies will provide and inform the directions of research into delirium in people with advanced cancer.

Abbreviations
BDNF: Brain-derived neurotrophic factor
CRP: C-reactive protein
CSF: Cerebrospinal fluid
ELISA: Enzyme-linked immunosorbent assay
IL-: Interleukin
NSE: Neuron specific enolase
S100B: S100B calcium binding protein B
TNF: Tumor necrosis factor

Declarations

Ethics approval and consent to participant
Not applicable.

Consent for publication
Not applicable.

Availability of data and material
All data generated or analysed in this systematic review are included within this published article and its additional files.
Competing interests
The authors declare that they have no competing interests.

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Authors contributions
IAD undertook the literature search, identified potential articles, extracted data, interpreted results, performed a quality assessment, drafted and revised all versions of the manuscript. MA and AM contributed to study selection and screening, interpreting results, revised manuscript drafts and supervised the study. All authors (IAD, AM, MA and GC) contributed to the interpretation of results, manuscript preparation and read and approved the final manuscript.

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Tables

Table 1. Characteristics of assays and main findings of included delirium studies*

| Author and year | Total (N) | Sample | Total participant s with cancer/tota l participant s in the study | Number of delirium with cancer/tota l number delirium (%) | Endpoints | Biomarkers studied |
|----------------|----------|--------|---------------------------------------------------------------|--------------------------------------------------------|----------|-------------------|
| Egberts et al. (2017) (34) | 86 | Aged ≥65 admitted to geriatrics | Not measured/N R | Not measured/N R | Delirium presence | CRP, NLR |
| Kozak et al. (2017) (31) | 60 | Patients with acute ischemic stroke | Not measured/N R | Not measured/N R | Delirium presence | TNF-α, IL-1β, IL-1 BDNF, NSE |
| Tomasi et al. (2017) (35) | 38 | Patients with sepsis-associated delirium and non-sepsis associated deliriuma | Not measured/N R | Not measured/N R | Delirium presence | IL-6, IL-8, IL-10, BDNF, VCAM-1, ICAM-1, MPO, cathepsin, PDGF-AA, PDGF-AB/BB, RANTES, PAI, NCAM |
| Vasunilashorn et al. (2017) (36) | 560 | Patients ≥70 undergoing major non-cardiac surgerya | Not measured/N R | Not measured/N R | -Delirium incidence | CRP |
| Chu et al. (2016) (37) | 103 | Patients aged ≥70 | Not measured/N | Not measured/N | Delirium incidence | IGF-1 |
| Study | Participants | Methods | Outcomes | Other Measurements |
|-------|--------------|---------|----------|-------------------|
| Dillon et al. (2016) (37) | Entire sample (n=566); pooled sample (n=150) | Dementia-free adults ≥70 years old undergoing major non-cardiac surgery<sup>a</sup> | Advanced cancer excluded; other cancer stages NR | Delirium incidence | Proteomics<sup>b</sup> |
| Guo et al. (2016) (38) | 572 | Aged ≥65 with hip fractures undergoing THA<sup>a</sup> | Not measured/NR | Delirium prevalence | CRP, Alb, Hb |
| Karlincic et al. (2016) (39) | 120 | Patients with delirium in the psychiatric ICU | None | Lethal outcome | CRP |
| Neerland et al. (2016) (40) | 149 | Patients with acute hip fracture | Advanced cancer excluded, other cancer stages NR | Delirium presence | CRP, IL-6, sIL-6R |
| Shen et al. (2016) (41) | 140 | Patients ≥65 undergoing elective gastrointestinal resection<sup>a</sup> | 140/140 (100) | Delirium incidence | IGF-1, CRP, IL-6 |
| Sun et al. (2016) (42) | 112 | Oral cancer patients<sup>a</sup> | 112/112 (100) | Delirium incidence | IL-6, CRP, PCT, cortisol, AB1-40 |
| Yen et al. (2016) (43) | 98 | Patients undergoing elective knee replacement surgery | Not measured/NR | Delirium incidence | IGF-1 |
| Avila-Funes et al. (2015) (44) | 141 | Patients aged ≥70 admitted to tertiary care hospital | 37/141 (26.2) | Delirium incidence | Cortisol, E2 |
| Brum et al. (2015) (45) | 70 | Oncology inpatients<sup>a</sup> | 45-70 (64.2) | Delirium presence | BDNF, TNF-α |
| Egberts et al. (2015) (46) | 86 | Patients admitted to Internal Medicine and Geriatrics<sup>a</sup> | Not measured/NR | Delirium presence | NP, IL-6, IGF-1 |
| Foroughan et al. (2015) (47) | 200 | Elderly patients | 18/200 (9) | Delirium presence | CRP, Hb |
| Authors                  | Participants | Study Details                                                                 | Measured Parameters                                                                 | Results                                                                 |
|-------------------------|--------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| Skrede et al. (2015)    | 10           | Patients admitted to general hospital                                            | MCP-1                                                                               | Delirium incidence                                                    |
| Vasunilashorn et al. (2015) | 566         | Patients ≥70 undergoing major non-cardiac surgery^a                            | Delirium incidence                                                                   | IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IFN-γ, GM-CSF, TNF-α, VEGF |
| Alexander et al. (2014) | 77           | ICU patients requiring mechanical ventilation                                    | Delirium incidence - Delirium duration                                             | IL-6, IL-8, IL-10, APOE                                               |
| Baranyi et al. (2014)   | 34           | Patients undergoing surgery for CPB^a                                           | Delirium incidence sIL-2R                                                             |                                                                        |
| Cape et al. (2014)      | 43           | Patients >60 years old with hip fracture                                         | Delirium incidence - Delirium prevalence                                             | IL-1β, IFN-γ, GFAl, IGF-1, IL-1RA                                     |
| Capri et al. (2014)     | 351          | Patients admitted for any kind of emergency or elective surgery^a              | Delirium presence                                                                     | IL-1β, IL-2, IL-6, IL-8, IL-10, TNF-α                                 |
| Chen et al. (2014)      | 372          | Patients aged ≥65 who underwent surgery for a femoral neck fracture or an intertrochanteric fracture^a | Delirium presence                                                                     | LP                                                                    |
| Hatta et al. (2014)     | 29           | Patients aged 65-89 admitted to hospital due to an emergency                    | Delirium incidence                      NK cell activity, IL 1β                                |
| Kazmierski et al. (2014) | 113         | ICU patients scheduled for CABG surgery with CPB                              | Delirium incidence                                 Cortisol, IL-2, TNF-α, HCY, cobalamin                           |
| Ritchie et al. (2014)   | 710          | Patients admitted to a Medical Acute Admission Unit                            | Delirium incidence - Delirium severity                                               | CRP                                                                   |
| Ritter et al. (2014)    | 78           | ICU patients                                                                  | Delirium presence                                                                     | TNF-α, STNFR-1, STNFR2, APN, IL-1β, IL-6, IL-10                       |
| Zhang et al. (2014)     | 223          | ICU patients                                                                  | Delirium presence                                                                     | CRP                                                                   |
| Study                  | N   | Patients Description                                                                 | Measured Parameters | Delirium Incidence | Biomarkers |
|-----------------------|-----|-------------------------------------------------------------------------------------|---------------------|-------------------|------------|
| Cerejeira et al.      | 101 | Patients ≥60 years without dementia undergoing elective hip arthroplasty<sup>a</sup> | Not measured/Not measured | Delirium incidence | Cortisol, IGF-1, CRP, IL-6, IL-8, IL-10 |
| Colkesen et al.       | 52  | Patients with ACS admitted to coronary ICU<sup>a</sup>                              | Not measured/Not measured | Delirium presence | Cortisol, troponin MB-CK |
| Kazmierski et al.     | 113 | ICU patients scheduled for CABG surgery with CPB<sup>a</sup>                        | Not measured/Not measured | Delirium incidence | Cortisol, IL-2 |
| Kazmierski et al.     | 113 | ICU patients scheduled for CABG surgery with CPB<sup>a</sup>                        | Not measured/Not measured | Delirium incidence | IL-2, TNF-α |
| Liu et al.            | 338 | Patients aged ≥60 undergoing major non-cardiac surgery<sup>a</sup>                  | Not measured/Not measured | Delirium incidence | IL-6 |
| Plaschke et al.       | 114 | 1. Patients following heart surgery<sup>a</sup> 2. Patients on the non-cardiac ICU<sup>a</sup> | Not measured/Not measured | Delirium incidence | IL-6 |
| Skrobik et al.        | 99  | ICU patients<sup>a</sup>                                                             | Not measured/Not measured | Drug-induced coma and delirium | TNF-α, IL-1β, IL-1RA, IL-6, IL-8, IL-10, IL-17, MIP-1β, MCP-1 |
| Westhoff et al.       | 61  | Patients ≥75 admitted for surgical repair of acute hip fracture<sup>a</sup>           | Not measured/Not measured | Delirium incidence | EGF, eotaxin, FGF-2, Flt-3L, Fractalkine, G-CSF, GM-CSF, IFN-α2, IFN-γ, IL-1RA, IL-1α, IL-1β, IL-2, sIL-2Ra, IL-3, IL-4, IL-6, IL-7, IL-8, IL-10, IL-12p40, IL-12p70, IL-13, IL-17, IP-10, MCP-MCP-3, MDC, MIP-1α, MIP-1β, PDGF AA, PDGF-AB/BB, RANTES, sCD40L, |

<sup>a</sup> Note: Not measured/Not measured/N R means that cortisol and IGF-1, CRP, IL-6, IL-8, IL-10 were not measured or recorded as not measured in the study. Delirium incidence indicates the presence of delirium.
| Study                  | N   | Population Description                                    | Biomarkers                                      | Delirium Measure   | Other Measures                        |
|-----------------------|-----|----------------------------------------------------------|------------------------------------------------|-------------------|---------------------------------------|
| Bakker *et al.* (2012) | 201 | Patients undergoing cardiac surgery                      | TGF-α, TNF-α, TNF-β, VEGF                      | Delirium incidence | Cre                                   |
| Baranyi *et al.* (2012) | 34  | Patients undergoing surgery for cardiopulmonary bypass   | Not measured/N R                                | Delirium incidence | Alb, CRP                              |
| Cerejeira *et al.* (2012) | 101 | Patients aged ≥60 undergoing elective total hip arthroplasty | Not measured/N R                                | Delirium incidence | IL-8, IL-1β, IL-6, IL-10, TNF-α, CRP, AChE, BuChE |
| Girard *et al.* (2012) | 138 | Mechanically ventilated ICU patients                      | Not measured/N R                                | Delirium incidence | CRP, MMP-9, MIP, NGAL, sTNFR1, D dimer, protein C, PAI-1, VWF |
| Osse *et al.* (2012)   | 125 | Patients ≥70 undergoing elective cardiac surgery         | Not measured/N R                                | Delirium incidence | NP, BH4, HVA, Glu, Gly, Cit, Tau, Arg, Met, Try, Tyr, Phe, Leu, Ile, Val, Try:LNAA, Ty:LNAA, Phe:LNAA, Phe:tyr, Cit:arg, Tau:Ser, Tyr:LNAA, Phe:tyr, Cit:arg, Tau:Ser |
| Bisschop *et al.* (2011) | 143 | Patients undergoing surgery for hip fracture             | Not measured/N R                                | Delirium presence  | Cortisol, insulin, glucose             |
| Holmes *et al.* (2011) | 222 | Patients with mild to severe AD                          | Not measured/N R                                | Presence of sickness behaviour | IL-6, TNF-α, CRP |
| Lee *et al.* (2011)    | 65  | Patients ≥65 who had undergone hip surgery               | Not measured/N R                                | Delirium incidence | CRP                                   |
| McGrane *et al.* (2011) | 87  | Mechanically ventilated,                                  | Not measured/N R                                | Delirium/coma-free days | PCT, CRP                             |
| Study                        | Sample Size | Study Population | Area Measured | Delirium | Other Measured |
|------------------------------|-------------|------------------|---------------|----------|----------------|
| Morandi et al. (2011)        | 110         | Mechanically ventilated medical ICU patients | Not measured/NR | Delirium presence | IGF-1 |
| Van der Boogaard et al. (2011)a | 100         | ICU patients | Not measured/NR | Delirium presence | TNF-α, IL-1β, IL-6, IL-8, IL-17, IL-18, MIF, IL-1RA, IL-10, MCP-1, HNP-1, CRP, PCT, Ab1-42, Ab1-40, S100B, cortisol |
| Van der Boogaard et al. (2011)b | 20          | ICU patients | Not measured/NR | Delirium presence | Proteomics |
| Burkhart et al. (2010)       | 113         | Patients aged ≥65 undergoing elective cardiac surgery with CPB | Not measured/NR | Delirium presence | CRP |
| Mu et al. (2010)             | 243         | Patients undergoing elective CABG surgery | Not measured/NR | Delirium incidence | Cortisol |
| Pearson et al. (2010)        | 20          | Patients ≥60 with acute hip fracture awaiting surgery | Not measured/NR | Delirium presence | Cortisol |
| Plaschke et al.              | 114         | Patients       | Not           | Delirium     | Cortisol, IL-6 |
| Study                                      | Sample Size | Participants | Measured Parameters | Other Parameters |
|-------------------------------------------|-------------|--------------|---------------------|------------------|
| al. (2010) (83)                           | 103         | ICU patients | Not measured/N R    | CRP              |
| Van Munster et al. (2010) (85)            | 120         | Patients ≥65 admitted for hip fracture surgery | Not measured/N R | Delirium presence |
| Adamis et al. (2009) (86)                 | 67          | Patients aged ≥70 admitted to elderly care unit | Not measured/N R | APOE, IL-1a, IL-1β, IL-1RA, IL-6, TNF-IGF-1, IFN-γ, LIF |
| Van Munster et al. (2009) (87)            | 120         | Patients ≥65 admitted for hip fracture surgery | Not measured/N R | Delirium incidence |
| Lemstra et al. (2008) (88)                | 68          | Patients undergoing surgery for hip fracture | Not measured/N R | S100B, NSE |
| Pfister et al. (2008) (89)                | 16j         | Patients with sepsis | Not measured/N R | CRP, IL-6, IGF-1 |
| Rudolph et al. (2008) (90)                | 42          | Patients undergoing cardiac surgery | Not measured/N R | IL-1β, IL-1RA, IL-6, IFN-α, TNF-α, TNF-R1, TNF-R2, IL-2, IL-2R, IL-7, IL-12p40, IL-10, IL-15, IFN-γ, IP-10, IL-4, IL-5, IL-10, IL-13, MIP-1a, MIP-1b, MIG, Eotaxin, RANTES, CCL-2, GM-CSF, IL-17, DR5 |
| Van Munster et al. (2008) (91)            | 98          | Patients ≥65 admitted for hip fracture surgery | Not measured/N R | IL-6, IL-8, IL-12 (TNF-α, IL-1β, and IL-10 excluded from analysis) |
| Adamis et al. (2007) (92)                 | 164         | Acutely ill patients admitted to elderly care unit | Not measured/N R | APOE, IL-1a, IL-1β, IL-1RA, IL-6, TNF-IGF-1, IFN-γ, LIF, CRP |
| de Rooij et al. (2007) (93)               | 185         | Patients aged ≥65 admitted to the Department of Medicine | 18/185 (9.7) | Delirium incidence |
| Plaschke et al. (2007) (94)               | 37          | ICU patients | Not measured/N R    | SAA, IL-6 |
| White et al. (2005) (95)                  | 283         | Patients ≥75 from emergency | Not measured/N R | CRP, Alb, AChE, BuchE, Aspirin esterase |
| Study                        | Participants | Medical History                                      | Incidence | Biomarkers  |
|------------------------------|--------------|-----------------------------------------------------|-----------|-------------|
| Wilson et al. (2005) (96)    | 100          | Patients ≥75 suffering from significant physical illness | Delirium incidence | IGF-1       |
| Beloosesky et al. (2004) (97)| 32           | Patients undergoing surgery for hip fracture         | Delirium incidence | CRP, FBG    |
| Robertsson et al. (2001) (98)| 172          | Patients <80 referred to the neuropsychiatric diagnostic unit with suspected dementia | Delirium presence | Cortisol    |
| Van der Mast et al. (2000) (99)| 296^k         | Patients admitted for elective cardiac surgery       | Delirium incidence | Try, Ile, Val, Met, Leu, Tyr, Phe, Ser cortisol |
| Van der Mast et al. (1999) (100)| 296           | Patients admitted for elective cardiac surgery       | Delirium incidence | Alb, cortisol, 5-H try, phe, val, leu, lle, try:tyr:phe |
| Gustafson et al. (1993) (30) | 155          | Stroke patients                                      | Delirium presence | Cortisol    |
| McIntosh et al. (1985) (101) | 7            | Male patients admitted to hospital for elective surgery | Delirium incidence | Cortisol, B-endorphin |

* Studies with both delirium and cancer participants are bolded; red coloured biomarkers indicate significance in multivariate analysis
a Dementia was an exclusion criteria

b Only CRP is reported from this study

c Only between incident and prevalent delirium

d Pre-operative and post-operative cortisol remained significantly increased in delirium, however, after controlling for pre-operative depression, only preoperative cortisol concentration remained significant, irrespective of the cortisol level after surgery.

e Only 66 included in the primary analysis

f In inflamed patients only

g In non-inflamed patients only

h Only CRP and Cre are reported

i Same cohort as Plaschke et al. 2007

j Only 16 were analysed

k same cohort as Van Der Mast et al. 1999

**Abbreviations:** 5HIAA: 5-Hydroxyindoleacetic acid; 5-HT: Serotonin; 6-SMT: 6-sulfatoxymelatonin; 8-Iso PGF2α: 8-iso-prostaglandin F2α; A1A: Alpha-1 antitrypsin; a-1-AGP: a-1-acid glycoprotein; AA: Anticholinergic activity; AB1: Amyloid-B; AChE: Acetylcholinesterase; ACS: Acute Coronary Syndromes; ADAS: Alzheimer’s Disease Assessment Scale; ADL: Activities of daily living; Ala: Alanine; Alb: Albumin; AD: Alzheimer’s Disease; APACHE: Acute Physiology and Chronic Health Evaluation; APN: Adiponectin; ANG: Angiopoietin; APOA1: Apolipoprotein A1; APOE: Apolipoprotein E; Arg: Arginine; APS: Acute Physiology Score; ASA: American Society of American Society of Anaestesiologists Scale; BCA: The bicinchoninic acid assay; BDNF: Brain-Derived Neurotrophic Factor; BH4: Tetrahydrobiopterin; BLI: B-Endorphin-Like Immunoreactivity; BuChE: Butyrylcholinesterase; C3: Complement C3; CABG: Coronary Artery Bypass Graft; CBA: Cytometric bead array immunoassay; CCI: Charlson Comorbidity Index; Cit: Citrulline; CK: Creatine Kinase; CK-MB: Creatine Kinase-MB;
CLIA: Chemiluminescence immunoassay; CNTN-1: Contactin-1; CPB: Cardiopulmonary Bypass; Cre: Creatinine; CRP: C-Reactive Protein; E2: Estrodiol; FBG: Fibrinogen; FBLN-1: Fibulin-1; ECLIA: Electrochemiluminescence immunoassay; EGF: Epidermal Growth Factor; FGF-2: Fibroblast Grown Factor; Flt-3L: FMS-like tyrosine kinase 3 ligand; GABA: Gamma-Aminobutyric Acid; G-CSF: Granulocyte Stimulating Factor; GFAP: Glial Fibrillary Acidic Protein; GHQ: General Health Questionnaire; Glu: Glutamic acid; Gly: Glycine; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; HADS: Hospital Anxiety and Depression Scale; Hb: Haemoglobin; HCY: Homocysteine; HNP-1: Defensin; HP: Haptoglobin; HPLC: High-performance liquid chromatography; HVA: Homovanillic Acid; IADL: Instrumental activities of daily living; ICU: Intensive care unit; Ile: Isoleucine; ICAM-1: Intercellular Adhesion Molecule 1; IDO: Indoleamine 2, 3-dioxygenase; IFN: Interferon; IGF: Insulin-Like Growth Factor; IL= Interleukin; IL-1RA: Interleukin-1 Receptor Antagonist; Ile: Isoleucine; IP-10: Interferon gamma-induced protein 10; IQCODE: The Informant Questionnaire on Cognitive Decline in the Elderly; KYN: Kynurenine; Leu: Leucine; LIF: Leukaemia Inhibitory Factor; LNAA: Large Neutral Amino Acids; LOS: Length of stay; LP: Leptin; Met: Methionine; MB-CK: MB-isoform of Creatinine Kinase; MCP: Monocyte Chemotactic Protein; MDC: Human Macrophage-derived Chemokine; MIF: Macrophage Migration Inhibitory Factor; MIG: Monokine induced by Gamma Interferon; MIP: Macrophage Inflammatory Protein; MMP-9: Matrix Metalloproteinase-9; MMSE: Mini-mental state examination; MPO: Myeloperoxidase; MT: Melatonin; NCAM: Neural Cell Adhesion Molecule; NGAL: Neutrophil Gelatinase-Associated Lipocalin; NLR: Neutrophil-Lymphocyte ratio; NK cells: Natural killer cells; NP: Neopterin; NR: Not reported; NSE: Neuron Specific Enolase; Orn: Ornithine; NYHA: New York Heart Association; PACU: Post-anesthesia care unit; PAI-1: Plasminogen activator inhibitor-1; PCT: Procalcitonin; PDGF: Platelet-Derived Growth Factor; Phe: Phenylalanine; pMHPG: Plasma free 3-methoxy-4-hydroxyphenylglycol; pNF-H: The Phosphorylated Neurofilament H; PO1MO: 1 month post-operative; POD2: Post-operative day 2; PONV: Post-operative nausea and vomiting; POST-OP: Post-operative; PRE-OP: Pre-operative; P-tau: Phosphorylated tau; RANTES: Chemokine (C-C motif) ligand 5; RBC: Red blood cell; S100B: s100 calcium-binding protein B; sCD40L: Soluble CD40 ligand; Ser: Serine; sIL-XR: Soluble IL-1 receptor; SLI: Somatostatin-Like Immunoreactivity; sTNFR: Soluble Tumor
Necrosis Factor Receptor; Tau: Taurine; T-tau: Total tau; TGF-a: Transforming Growth Factor Alpha; THA: Total Hip Arthroplasty; TRACE: Time Resolved Amplified Cryptate Emission; TSH: Thyroid Stimulating Hormone; TNF: Tumor Necrosis Factor; Trp: Tryptophan; TRX: Thioredoxin; Tyr: Tyrosine; UDL: Under detection limit; Val: Valine; VCAM-1: Vascular Cell Adhesion protein 1; VEGF: Vascular Endothelial Growth Factor; vWF: Von Willebrand factor; ZAG: Zinc-a-2-Glycoprotein

Table 2. Characteristics of assays and main findings of included cancer studies*

| Author and year | Participants | Endpoints | Biomarkers studied | Biological material |
|-----------------|--------------|-----------|--------------------|--------------------|
| Amano et al. (2017)\(^\circ\) (102) | 1702 | Advanced cancer patients; no control | -Anorexia  
-Weight loss  
-Fatigue  
-Dyspnea  
-Dysphasia  
-Edema  
-Pressure ulcer  
-ADL disabilities | CRP | NR |
| Demiray et al. (2017) (103) | 87 | Participants with advanced cancer; healthy participants without a known chronic disease | -Cachexia  
-Weight loss  
-PFS  
-OS | LP, resistin | Serum |
| Fogelman et al. (2017) (104) | 69 | Participants with advanced cancer; healthy controls with no cancer diagnosis | Either 10% weight loss or death at 60 days from the start of therapy | APN, bFGF, CXCL-16, FSN, Ghrelin, IGF-1, IL-1β, IL-6, IL-8, Klotho, LP, MCP-4, MK, MSTMN, PIF, sTNFR1, sTNFR2, TARC, TNF-α, VEGF, ZAG | NR |
| Luo et al. (2017) (105) | 217 | Participants with advanced cancer; no control | -PFS  
-OS | FBG, CA-125, NLR, PLR | Serum + Plasma |
| Paulsen et al. (2017) (106) | 49 | Participants with cancer; no control | -Pain  
-Appetite  
-Fatigue | CRP, ESR, sTNF-R1, IL-1RA, IL-6, MCP-1, IL-18, MIF, TGF-β1 | Serum |
| Amano et al. (2016) (107) | 1511 | Advanced cancer patients; no control | -Survival rate  
-Mortality rate | CRP | Plasma |
| Bye et al. (2016) (108) | 60 | Participants with advanced cancer; healthy controls with normal weight | -Cachexia  
-Survival | IL-10, IFN-γ, LP, APN, TNF-α, IL-6, IGF-1 | Serum |
| Mitsunga et al. (2016) (109) | 421 | Participants with advanced cancer with low, | OS | CRP, NLR | Blood |
| Study                        | Participants | Description                                                                 | Biomarkers                     | Samples |
|------------------------------|--------------|-----------------------------------------------------------------------------|--------------------------------|---------|
| Morgado et al. (2016) (110)  | 49           | Participants with advanced cancer and fatigue with and without weight loss  | -Weight loss, Fatigue          | Serum + Urine |
| Rodrigues et al. (2016) (111)| 51           | Participants with advanced cancer; no control                              | Fatigue                        | Blood   |
| Srdic et al. (2016) (112)    | 100          | Participants with advanced cancer and without cachexia                      | -Cachexia, Chemotherapy toxicity, Survival | NR      |
| Wu et al. (2016) (113)       | 55           | Participants with advanced cancer; no control                              | -OS, -PFS                      | Blood   |
| Bilir et al. (2015) (114)    | 80           | Participants with advanced cancer and cachexia; healthy controls with no known chronic disease or weight loss | -OS, -Cachexia                 | Serum   |
| Miura et al. (2015) (115)    | 79           | Participants with advanced cancer; no control                              | -Body composition, Fatigue     | Serum   |
| Miura et al. (2015)b (116)   | 1160         | Participants with advanced cancer; no control                              | Survival                       | NR      |
| Barrera et al. (2014) (117)  | 135          | Participants with advanced cancer; healthy controls                        | -Quality of life (fatigue, PS, hyporexia, BMI), Survival | Plasma |
| Blakely et al. (2014) (118)  | 50           | Participants with advanced cancer with normal CRP and elevated CRP          | -OS, -Mortality rate, -gastrointestinal obstruction, -Pain, -Bleeding, -Other symptoms (NR), -Major complications | Serum   |
| Fujiwara et al. (2014) (119) | 21           | Participants with advanced cancer with and without cachexia                | Cachexia                       | Serum   |
| Lindemann et al. (2014) (120)| 218          | Participants with advanced cancer; no control                              | -Survival, -Weight loss        | Plasma   |
| Mondello et al. (2014) (121) | 170          | Participants with advanced cancer; healthy controls                        | -Survival, -Cachexia           | Serum   |
| Moriwaki et al. (2014) (122)| 62           | Patients with advanced cancer with GPS 0, GPS 1 or GPS 2                   | OS                             | NR      |
| Study                  | Sample Size | Study Population                                                                 | Outcome Measures                                                                 | Biomarkers          | Matrix    |
|-----------------------|-------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------|-----------|
| Szkandera et al. (2014) (123) | 474         | Participants with cancer; no control                                              | Cancer-specific survival                                                           | CRP, NLR, PLR       | Plasma    |
| Zhang et al. (2014) (124) | 200         | Participants with cancer; no control                                              | Fatigue; Chemotherapy adverse effects                                             | TNF-α, IL-1α, IL-1β, 17-HCS | Plasma + urine |
| Jafri et al. (2013) (125)   | 173         | Participants with advanced cancer with high inflammation and low inflammation    | PFS; OS                                                                          | ALI (Alb+NLR)       | Serum     |
| Laird et al. (2013) (126)   | 1466        | Participants with advanced cancer with low and high CRP levels                   | Symptoms of the EOTC (pain, appetite loss, cognitive function, dyspnea, fatigue, physical function, role function, social function, QoL, nausea/vomiting, diarrhea, sleep, constipation) | CRP                 | Blood     |
| Laird et al. (2013)b (127)  | 2456        | Participants with advanced cancer; no control                                     | Symptoms of the EOTC (pain, appetite loss, cognitive function, dyspnea, fatigue, physical function, role function, social function, QoL, nausea/vomiting, diarrhea, sleep, constipation) | mGPS (Alb+CRP)      | Blood     |
| Paiva et al. (2013) (128)   | 223         | Participants with cancer with and without fatigue                               | Fatigue; OS                                                                      | CRP, Hb, LDH, Alb   | Blood     |
| Suh et al. (2013) (129)     | 98          | Participants with advanced cancer; no control                                     | Survival                                                                         | IL-6, TNF-α         | Plasma    |
| De Raaf et al. (2012) (130) | 92          | Participants with advanced cancer; cancer survivors                              | Physical and mental fatigue                                                       | CRP, IL-1-RA, NP, IL-6 and IL-8 | Plasma    |
| Gioubasianis et al. (2012) (131) | 114         | Participants with advanced cancer with malnutrition, with a risk of malnutrition, and who were well nourished | Nutritional status (cachexia); Survival                                           | IL-8                | Plasma    |
| Gulen et al.             | 88          | Participants with weight loss (>5%)                                              | LP, APN, TNF-α, CRP                                                             |                     | Serum     |
| Reference | Study Population | Study Design | Outcomes | Biomarkers Measured | Study Sample Size | Body Fluid | Methodology |
|-----------|-----------------|--------------|----------|---------------------|------------------|------------|-------------|
| Heitzer et al. (2012) (133) | Advanced cancer patients with and without weight loss; age- and sex-matched controls | Pain intensity | IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, TNF-β, IFN-γ, IL-1α, IL-7, IL-13, IL-18, MCP-1, MIP-1α, MIP-1B, OPG | Serum | 65 |
| Minton et al. (2012) (134) | Participants with advanced cancer with and without fatigue | Fatigue | CRP, Alb, Hb | Blood | 720 |
| Partridge et al. (2012) (135) | Patients with advanced cancer with GPS 0, GPS 1 or GPS 2; no control | Survival | mGPS (Alb+CRP) | Blood | 102 |
| Pond et al. (2012) (136) | Participants with advanced cancer; no control | Survival | CRP | NR | 220 |
| Wang et al. (2012) (137) | Participants with cancer; no control | Survival | CRP, Alb, mGPS (Alb+CRP), NLR | NR | 177 |
| Aydin et al. (2011) (138) | Advanced cancer patients; no control | Survival | CRP, Alb, TFN | Serum | 61 |
| Dev et al. (2011) (139) | Participants with advanced cancer; no control | Symptom distress (pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, dyspnea, sleep) | Cortisol | Serum | 77 |
| Gioulbasanis et al. (2011) (140) | Participants with advanced cancer with malnutrition, with a risk of malnutrition, and who were well nourished | Nutritional status (cachexia) | Alb, CRP, ghrelin, LP, APN, IGF-1 | Plasma | 115 |
| Hwang et al. (2011) (141) | Participants with cancer; no control | -PFS -OS | Alb, CRP | Serum | 402 |
| Kwak et al. (2011) (142) | Participants with advanced cancer; no control | Fatigue | IL-6, TNF-α | Blood | 90 |
| Authors                      | n   | Participants with cancer | Outcomes                     | Markers                      | Matrix |
|------------------------------|-----|--------------------------|------------------------------|------------------------------|--------|
| Lee et al. (2011) (143)      | 126 | Participants with advanced cancer; no control | 14 day mortality            | CRP                          | Serum  |
| Scheede-Bergdahl et al. (2011) (144) | 83  | Participants with advanced cancer; no control | - Clinical features of cachexia (weakness, loss of appetite, fatigue, QOL, weight loss) -Survival | IL-6, IL-1β, IL-8, TNF-α | Plasma |
| Vlachostergios et al. (2011) (145) | 77  | Participants with advanced cancer; no control | -TTP -OS                    | IGF-1, CRP, Alb              | Serum  |
| Diakowska et al. (2010) (146) | 218 | Participants with cancer with and without cachexia; healthy blood donors; and patients with non-malignant diseases of alimentary tract | Cachexia            | LP, CRP, IL-1, IL-6, IL-8, TNF-α, Alb, Hb. | Serum  |
| Meek et al. (2010) (147)     | 56  | Participants with advanced cancer; no control | Cancer-specific survival | IGF-1, IGFBP-3, CRP, mGPS (Alb+CRP), LP | Serum  |
| Ishizuka et al. (2009) (148) | 112 | Participants with advanced cancer; no control | Mortality                 | CRP, Alb, mGPS (Alb+CRP), Neutrophil ratio | Serum  |
| Karapanagioto et al. (2009) (149) | 161 | Participants with advanced cancer; healthy controls | -Weight loss -TTP -OS | Ghrelin, LP                  | Serum  |
| Paddon et al. (2009) (150)   | 44  | Participants with advanced cancer; healthy controls | Fatigue                     | Hb, WBC, Neutrophil, Monocyte, Lymphocyte | Blood  |
| Takahashi et al. (2009) (151) | 26  | Participants with cancer cachexia; healthy controls | Anorexia (cachexia and BMI) | TNF-α, IFN-γ, IL-6, IL-1RA, LP, ghrelin | Plasma |
| Inagaki et al. (2008) (152)  | 46  | Participants with advanced cancer with and without fatigue | Fatigue                     | IL-6                        | Plasma |
| Karapanagioto                | 152 | Participants with           | -Weight loss                | LP, APN, resistin             | Serum  |
| Reference                       | Participants | Description                                                                 | Markers                                                                 | Media          |
|--------------------------------|--------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------|----------------|
| u et al. (2008) (153)          |              | advanced cancer; healthy controls                                          | -TTP -OS                                                               | Serum          |
| Sharma et al. (2008) (154)     | 52           | Participants with advanced cancer; no control                              | IL-1β, IL-2, IL-4, IL-5, IL-8, IL-6, IL-10, IL-12, GM-CSF, IFN-Y, TNF-α, sIL-6R, sgp130, VEGF, eotaxin, MCP-1, MIP-1α, MIP-1β, Alb, CRP, GPS (Alb+CRP) | Serum          |
| Weryńska et al. (2008) (155)   | 40           | Participants with advanced cancer with and without cachexia                | -Cachexia -Nutritional status                                         | Serum          |
| Ravasco et al. (2007) (156)    | 101          | Participants with cancer; no control                                        | IL-1RA, IL-6, TNF-α, IL-10, IFN-γ, VEGF                                | Serum          |
| Richey et al. (2007) (157)     | 24           | Participants with cancer with and without cachexia                         | GPS (Alb+CRP), Alb, IL-1a, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α, IFN-γ, VEGF, GM-CSF, MCP-1, MIP-1α, MIP-1β, RANTES, FGF, Hb, CRP, CEA | Serum          |
| Suh et al. (2007) (158)        | 44           | Participants with advanced cancer; no control                              | Survival                                                               | CRP            |
| Al Murri et al. (2006) (159)   | 96           | Breast cancer patients; no control                                         | Survival                                                               | CRP, Alb, GPS (Alb+CRP) | NR            |
| Kayacan et al. (2006) (160)    | 56           | Participants with advanced cancer with and without cachexia; healthy smokers for the control | -Cachexia -PS -Survival                                               | TNF-α, IL-6    | Serum         |
| Ramsey et al. (2006) (161)     | 119          | Participants with advanced cancer; no control                              | -Cancer-specific survival -Cancer-specific mortality                  | GPS (Alb+CRP)  | NR            |
| Di Nisio et al. (2005) (162)   | 141          | Participants with advanced cancer; no control                              | Survival                                                               | IL-6, IL-10, IFN-γ, P-selectin | Plasma       |
| Rich et al. (2005) (163)       | 80           | Participants with advanced cancer with good and dampened circadian rhythms | -Extent of metastatic disease -PS -QOL                                | IL-6, TGF-α, TNF-α, cortisol | Serum        |
| Bolukbas et al. (2004) (164)   | 69           | Participants with advanced cancer; healthy controls with stable weight     | Weight loss                                                            | LP             | Serum         |
| De Vita et al. (2004) (165)    | 68           | Participants with advanced cancer; no control                              | -TTP -OS                                                               | IL-6           | Serum         |
| Dulger et al. (2004) (166)     | 54           | Participants with advanced cancer with and without cachexia; healthy gender- and age-matched adults | Cachexia                                                              | TNF-α, IL-1β, IL-6, CRP, LP, GH, TG, insulin, glucose, triglyceride, total protein, ESR | Serum         |
| Elahi et al. (2004) (167)      | 165          | Participants with advanced cancer; no control                              | Survival                                                               | Alb, CRP       | NR            |
| Jamieson et al.                | 33           | Participants with advanced cancer; no control                              | Weight loss                                                            | Hb, Alb, CRP, APN, | Serum        |

**NR** indicates not reported.
| (2004) (168) | advanced cancer; healthy controls | -Malnutrition -Survival | LP, IL-6 |
|------------|----------------------------------|-------------------------|---------|
| Songur et al. (2004) (169) | 91 | Participants with advanced cancer; healthy controls | IL-6, Alb, CRP, TFN, LDH | Serum |
| Scott et al. (2003) (170) | 106 | Participants with advanced cancer with and without weight loss | Hb, Alb, CRP | Blood |
| Aleman et al. (2002) (171) | 106 | Patients newly diagnosed with NSCL vs patients with no cancer | IL-6, IL-12, IL-10, IL-2, LP, α -1A, ferritin, CRP, TNF-α, s-TNFR2, s-IL-2R, IFN-γ | Serum |
| Orditura et al. (2002) (172) | 85 | Participants with advanced cancer; healthy controls | IL-8, IL-10, IL-2 | Serum |
| Scott et al. (2002) (173) | 106 | Participants with advanced cancer; no control | Alb, CRP | Blood |
| Jatoi et al. (2001) (174) | 73 | Participants with advanced cancer; healthy controls | NPY, LP, CCK-8 | Serum |
| Mantovani et al. (2001) (175) | 58 | Participants with advanced cancer; normal weight healthy controls | LP, IL-6, TNF-α | Serum |
| Mantovani et al. (2000) (176) | 32 | Participants with advanced cancer; normal weight healthy controls | LP, IL-1a, IL-6, and TNF-α | Serum |
| Nenova et al. (2000) (177) | 87 | Participants with advanced cancer; healthy controls | TNF-α | Serum |
| O’Gorman et al. (1999) (178) | 50 | Participants with advanced cancer with weight loss or weight gain; weight stable controls | Alb, CRP | Blood |
| Okada et al. (1998) (179) | 100 | Participants with cancer; healthy controls | IL-6 | Serum |
| Wallace et al. (1998) (180) | 54 | Participants with advanced cancer; healthy controls | LP | Serum |
| Maltoni et al. (1997) (181) | 530 | Participants with advanced cancer; no control | Neutrophil, lymphocyte & monocyte %, basophil + eosinophil %, Hb, TFN, Alb, total WBC, Pseudocholinesterase, proteineuria, TFN, transport iron | Blood |
| Simons et al. (1997) (182) | 21 | Participants with cancer and weight loss; no control | LP | Plasma |
Note: Cancer prognosis was not separated from the other syndromes in the table

* Red coloured biomarkers indicate significance in multivariate analysis

\[ a \] Secondary analysis of Amano, 2016

\[ b \] In cancer vs no cancer only

Abbreviations: 17-HCS = 17-hydroxycorticosteroids; \( \alpha \)-1-AGP: \( \alpha \)-1-acid glycoprotein; \( \alpha \)-1A: alpha-1 antitrypsin; Alb: Albumin; ALP: Alkaline phosphatase; APN: Adiponectin; APOA2: Apolipoprotein A2; BCA: The bichinonic acid assay; bFGF: Basic fibroblast growth factor; CA 19-9: Cancer antigen; CBA: Cytometric bead array immunoassay; CCK: Cholecystokinin; CEA: Carcinoembryonic antigen; CK: Creatine Kinase; CLIA: Chemiluminescence immunoassay; Cre: Creatinine; CRP: C-Reactive Protein; CXCL: Soluble CXC chemokine ligand; ESR: Erythrocyte sedimentation rate; FBG: Fibrinogen; FSN: Follistatin; GH: Growth Hormone; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; HA: Hyaluronic Acid; Hb: Haemoglobin; IGF: Insulin-Like Growth Factor; IGFBP: Insulin-like Growth Factor Binding Protein; IL: Interleukin; IFN: Interferon; LDH: Lactate Dehydrogenase; LP: Leptin; MCP: Monocyte Chemotactic Protein; MIP: Macrophage Inflammatory Protein; MK: Midkine; NI: Not enough information; NR: Not reported; MSTN: Myostatin; NLR: Neutrophil-lymphocyte ratio; NP: Neopterin; NPY: Neuropeptide Y; OPG: Osteoprotegrin; PLR: Platelet-lymphocyte ratio; RANTES: Chemokine (C-C motif) ligand 5; sTNFR: SolubleTumor Necrosis Factor Receptor; Sgp130 = Soluble **glycoprotein** 130; TARC: Thymus and Activation-Regulated Chemokine; TFN: Transferrin; TG: Triglyceride; TNF: Tumor Necrosis Factor; TRAF-6: Tumor Necrosis Factor Receptor associated factor-6; TTF: Time to treatment failure; TWEAK: TNF-like weak inducer of apoptosis; VEGF: Vascular Endothelial Growth Factor; ZAG: Zn-alpha2 glycoprotein

**Additional File Legends**

**Additional file 1:**
Format: Microsoft Word
Title: MEDLINE search strategies
Description: MEDLINE search strategies for delirium and cancer studies

**Additional file 2:**

Format: Microsoft Word

Title: Participant characteristics- delirium studies

Description: Characteristics of participants in the included delirium studies

**Additional file 3:**

Format: Microsoft Word

Title: Participant characteristics- cancer studies

Description: Characteristics of participants in the included cancer studies

**Additional file 4:**

Format: Microsoft Word

Title: Quality assessment of included delirium studies using the REMARK checklist

Description: The quality assessment for all included delirium studies

**Additional file 5:**

Format: Microsoft Word

Title: Quality assessment of included cancer studies using the REMARK checklist

Description: The quality assessment for all included cancer studies

**Additional file 6:**

Format: Microsoft Word

Description: PRISMA checklist

Figures
Figure 1
PRISMA flow diagram of search results
Conceptual model illustrating the ‘true overlap’ of delirium and advanced cancer biomarker studies. * Cancer as a comorbidity not measured/reported # Delirium as a concurrent illness or comorbidity not measured/reported

Figure 3
Quality assessment graph of the assay procedures: review author’s judgements about each assay domain of the REMARK checklist, presented as percentages across studies.

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.
Additional file 5- cancer quality assessment.docx
Additional file 6_PRISMA_checklist_13.08.19.doc
Additional file 4- Delirium quality assessment.docx
Additional file 3 cancer study characteristics.docx
Additional file 1_Search strategies.docx
Additional file 2- delirium study characteristics_Revised.pdf