The time factor as an associative concept relation in modelling post-liver transplant management complications

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Abstract

We propose a first termontological analysis of temporal parameters and relations applied to the case of medical complications in post-liver transplant management (PLTM). Medical complications contribute to different degrees of morbidity and mortality in the process of medical follow-up after transplant surgery. Understanding the full ontological and conceptual complexity of such complex spanning (SPAN) time events time is a central issue in drawing an implementable semantic map of the potential causes of early and long term complications, their diagnosis and the potential effects due to medical treatment. The analysis is usage-based and relies on linguistic utterances for complications in a concise medical review article.

1 Intro: medical complications and associative relations in termontology

This paper deals with medical complications and their termontological description. Termontology (Roche, 2007) combines insights from terminology and applied ontology, combining them with a linguistic dimension: whereas terminology is basically interested in complex tree representations between terms and their normalized definitions, applied ontology models (visual) representations of complex concept systems, including semantic relations that dynamically connect static entities in a terminological database. This paper combines both preoccupations, starting from descriptions of medical complications, more specifically those occurring in post-liver-transplant management (PLTM). In the area of liver transplantation, termontology improves understanding of conceptual structures based on the lexico-grammatical structures retrieved from scientific literature about complications following transplantation. So far, medical complications have not been the subject of much analysis in terminological or applied ontology. Yet, they represent a rich resource for investigating cause-effect relations that constitute a specific subcase of causal events. In a broader sense, a complication is any adverse, undesired and unintentional result of disease management. More technically, medical complications are iatrogenic (i.e. disease-related) subsets of cause-effect relations and refer to the (negative, adverse) morbid consequence of a disease or disorder resulting from unsuccessful disease management. Complications, occasionally known as suboptimal (negative) outcome, are not to be confused with sequelae of previous acute medical conditions and therapies. Negative outcomes can be subdivided into failure to cure (pre-existing conditions that remain unchanged after the transplantation procedure), negative sequel and complication (Clavien et al., 2006). Complications differ from the commonly expected sequelae resulting from an anterior acute medical condition and therapy. Understanding and dealing efficiently with postsurgical medical complications is a crucial issue for the improvement of healthcare quality, since complications require longer and more expensive treatment, and, more importantly,

will negatively affect patient prognosis. In extreme cases, they may lead to severe co-morbidity and even death.

Concept relations are a key concept in knowledge representation, because they interconnect the different concepts or entities in a given knowledge domain. Despite extensive work on concept relations (e.g. Khoo and Jin-Cheon, 2006), a descriptive, usage-based account of associative relations is lacking to date (Sambre and Wermuth, 2010). In the termontological approach, the focus has been on (static) hierarchical concept relations such as type-token and/or meronymic relations.

Biomedical terminology uses these vertical relations for unique designations of medical concepts and their terminological variants that result in a compendium of several controlled vocabularies such as the Unified Medical Language System (UMLS) and the controlled thesaurus of Medical Subject Headings (MeSH) (Grabar et al., 2012). These classifications display conceptual and so-called static snap shots of medical events. Biomedical ontologies, conversely, aim to explore snap shot relations against a dynamic background of temporal unfolding, which results in so-called SPAN (or spanning time) relations. This approach reflects the true conditions as medical concepts simultaneously express both hierarchical and associative (i.e. time-based) relations. The dynamicity of medical concepts is a phenomenon that deserves further study. In this paper, we therefore investigate in greater detail dynamic associative relations, focusing on the temporal underpinnings of causality in medical complications in post-liver transplant management (PLTM). The rationale is that causes, by definition, precede effects both from a logical and experiential perspective. Thus, the medical complications under investigation can be assumed to entail both causal and time-related relations. Our primary objective is to set out temporal parameters to be used in a conceptual model and to inventory specific associative time elements inherent to the concept of medical complication in PLTM.

2 Time in the conceptual map of medical complications

Time, in our view, is the underlying conceptual basis or background against which causality of (un)intentional medical events occur, as these events are or are not triggered by instrumental actions performed by medical teams. The following example taken from a specialized journal on transplantation in medicine should help to illustrate our objective. The example discusses a complication in PLTM, i.e. hepatic artery thrombosis (HAT): "[…] hepatic artery thrombosis (HAT) is the second main cause of liver graft failure. Moreover, HAT is the most common vascular complication in orthotopic liver transplantation (OLT). It is associated with a marked increase in morbidity, being the leading cause of graft loss (53%) and mortality (33%) during the immediate postoperative period. […] the consensus definition for early HAT was an arterial thrombosis detected during the first month after OLT. Late HAT was also defined as the event detected ≥ 1 month after OLT. […] The true incidence of early HAT is unknown, but it varies between 0% and 42%. […] improvements in postoperative care have led to a marked reduction in its incidence." (Pareja et al., 2010)

As can be seen from the example, there is clear linguistic evidence of both hierarchical and associative relations. The following observations can be made:

1. The linguistic expression (italics) designating the most common vascular complication, *the hepatic arterial thrombosis*, refers to a hierarchical type of thrombosis (kind_of relation).
2. Causal information is provided by the linguistic expressions *cause of liver graft failure, cause of graft loss and mortality.*
3. Implicit instrumental reference is made to the medical treatment in (complex) nouns such as *liver transplantation, graft failure* and *postoperative care*.
4. Temporal relations are set up between the medical treatment and the post-surgery adverse effect by means of prepositions expressing a relation of time such as *during the immediate postoperative period*, *during the first month after OLT*, or *≥ 1 month after OLT*.

From the above we can conclude that in medical discourse recurrent, grammatically complex linguistic patterns are used in order to connect (1) the entities and types, (2) the causes and (unintended) effects of health care, as well as (3) the instrumental treatment administered by medical doctors against a sequential background of (4) time. The interplay between these four kinds of relations may serve as a lexico-grammatical starting point for drawing up a conceptual map of the medical subdomain under investigation.

Such conceptual maps are fundamental for improving general procedures (in English) regarding

complications for medical care in **multi**disciplinary medical treatment. PLTM occurs in hospital teams, where physicians and nurses specialized in complementary fields of haematology, radiology, internal medicine, surgery and intensive care etc., collaborate in order to improve survival rates and reduce the impact of complications. Patient-centered healthcare implies collaborative settings that call for efficient IT support systems to monitor patient status and share information on the needs of patients. These maps are to be shared between the healthcare team's actors, providing the scenarios they share and the input of each team section or member based on their individual knowledge levels, their educational training, and the different services and platforms these persons work in.

3 A usage-based account of the conceptual structure of time

Our goal is to pinpoint the major dimensions of time in the description of complications in PLMT. For reasons of concision, we base our depiction on an often-quoted review article about PLTM (Moreno and Berenguer, 2006), a common genre in the medical scholar tradition, that summarizes available data for a given medical phenomenon. The article under investigation provides an overview of allograft dysfunctions and surgical complications following liver-transplant and discusses the state-of-the art concerning their medical follow-up. Strikingly, the article conceptually opposes immediate and long-term complications. These complications are of a different nature: they can be strictly medical (think of respiratory changes, renal dysfunction or hemodynamic complications), or technical (complications due to h(a)emorrhage or vascular complications resulting, for example, in infections or draft dysfunctions (major complications in this particular case are acute cellular rejection or recurrent viral hepatitis)). Both short and long-term complications are rather heterogeneous as well, due to the fact that the liver interacts with very different subsystems of the organism, whereby any dysfunction may cause diseases such as chronic rejection, arterial hypertension, obesity or bone complications, just to name a few. Our investigation is limited to the temporal aspects of the different complications, leaving aside other conceptual aspects such as anatomical location or severity.

3.1 Peri- and post-operative time

A first important time factor is the distinction between treatment peripheral to the central (intra-operative) transplant intervention that can have a direct impact on the reduction of post-surgical complications (Junttila et al., 2005), and the time lapse proper to the complication itself (the so-called post-operative time). Peri-operative time has to do with non-problematic follow up of surgery, before, during and after surgery. The difference between this peri- and post-operative time is minimal, given the fact that some complications such as infections may arise due to improperly performed medical actions:

(1) The prophylaxis of bacterial infection includes the following strategies: a) selective intestinal decontamination; b) administration of systemic antibiotics peri-operatively, c) antibiotic prophylaxis before invasive explorations of the biliary tract, and d) personnel hand washing together with strict asepsis in all invasive procedures.

The following observations can be made about example (1): strategies a), b) and c) in the example refer to such perioperative precautions. As a part of medical prevention, peri-operative treatment contributes to building the temporal barrier *ab quo* the time sequence of complication starts to run. Preventive, pre-operative treatment is an important time issue that should be taken into account in modelling medical complications: a distinction is needed between pre-symptomatic (example 2) and post-symptomatic treatment of complications. Prophylaxis aims at non-invasive avoidance of complication outbreak (example 3) and therefore reduces medical cost (example 4).

(2) Another form of prevention, mainly targeted to avoiding the development of clinically manifest CMV disease, is the treatment of infection in the pre-symptomatic stage. [81; note of the authors: CMV refers to cytomegalovirus, the most frequent micro-organism in liver transplantation]

(3) Universal prophylaxis is useful mainly in high-risk patients […] and can be done effectively and safely with oral drugs […]. [81]

(4) Anticipated treatment is also an effective and probably most cost-effective strategy.

The distinction between peri- and post-operative time as classification parameter is a central issue in the temporal (when do problems occur?), causal (what effects are produced?) and instru-

mental (what therapy positively affects such effects?) format of medical decision-making. In medical discourse, peri-operative techniques are explicitly juxtaposed to post-operative care, as the following example shows.

(5) The results of liver transplantation have improved due to advances in perioperative technique, a better understanding of the course and prognosis of several [sic] liver disease improved immunosuppressive therapy and more effective postoperative care. [77]

In fact, knowledge about postoperative complications is actively used in optimal peri-operative treatment.

A second time factor at the interface between peri-operative management and post-operative complications is the moment of detection of (early) complication symptoms. Detection and diagnosis of new symptoms clearly marks the distinction between prophylaxis and post-operative care. The following excerpt illustrates this distinction:

(6) Thus, knowledge of complications that emerge during follow up period, early and accurate establishment of diagnosis, and prompt institution of appropriate interventions are essential for optimal patient and graft outcome [77]

An important part of the state-of-the-art consists in describing so-called early detection methods such as in the following example:

(7) Methods for early detection of viral infection, in the case of cytomegalovirus, are periodic determination of CMV antigenemia in peripheral blood leukocytes and PCR techniques to detect the blood viral genome.

Defining medical states is a central issue in liver transplant surgery. The literature defines the normal state in the intensive care unit, after transplantation that shows increasing degrees of recovery as illustrated in the following example by the different modified verbal and nominal phrases:

(8) When the transplant evolves favorably, the patient is awake, hemodynamically stable, with spontaneous respiration, preserved renal function, and with progressively improving liver activity.

3.2 Time of occurrence: immediate and long-term

Complications are possible alterations to the desired optimal condition. The most frequent in PLTM are complications that can be expected during this early post-transplant period are hemodynamic alterations, and respiratory, renal and neurological complications.

A global distinction is the one between early and late complications, or more correctly, between immediate and long-term complications. Late complications are gaining importance as survival rates during the early-postoperative period increases. The distinction between complication subtypes is based on the point of their occurrence in time:

(9) The complications occur either immediately post-transplantation or in the long-term. The main complications in the immediate postoperative period are related to the function of the graft (dysfunction and rejection), the surgical technique, infections (bacterial, fungal, and viral), and systemic problems (pulmonary, renal, or neurological). In the long term, the complications are typically a consequence of the prolonged immunosuppressive therapy, and include diabetes mellitus, systemic arterial hypertension, de novo neoplasia, and organ toxicities, particularly nephrotoxicity.

An important note is that the underlying pathology causing the transplantation is not considered a complication, though the causal trigger may persist (or reemerge at some later point in time).

The definition or discursive description of complications typically contains the designation of the medical phenomenon, a general characterization in terms of immediate or late occurrence, followed by a more precise time label for the time span within which complications arise (in terms of hours, as in (10), days, or, in the case of late complications, months).

(10) A hemorrhage in the immediate postoperative period is another potential complication […].It is typically diagnosed within the first 48 hours post-transplantation (hemorrhagic abdominal drainages, hemodynamic instability, serial determination of the hematocrit/hemoglobin).

In the above example, the time label is followed by a summary of medical actions performed during this time lapse. Modelling complications then may entail two different time lines: one for occurrence of complications as such (snap and span, notions defined in the introduction of this paper), and one mapping the full (linear or cyclical) scenario of common medical actions associated with postoperative care.

The review article also mentions a shift in the historical evolution of PLTM complications: as surgical techniques and immunosuppressive treatment improve, prognosis and survival chances increase, correspondingly extending the time span of (late) medical post-surgical follow-up (cfr. (11) and (12)).

(11) The main barriers to overcome in the first period were immediate post-surgical survival together with prevention of acute rejection.

(12) With greater survival of patients, new problems have arose that basically affect transplant recipients with long-term follow up

Long-term complications are rather flexible conceptual notions. Their emergence is connected with the specific complication (such as chronic renal failure, systemic arterial hypertension, diabetes mellitus, etc.), but at the same time differs accordingly. Generic time information is commonly expressed as occurring at a random moment (13), or by means of unspecified post-operative time (14).

(13) […] malignant tumors can appear at any time after transplantation […].

(14) A variable percentage of patients, 4-20% according to the series, will develop diabetes mellitus following transplantation (de novo DM).

Apart from these general time labels, also different discursive strategies are used for indicating a precise moment in time, specifically in late complications. Here, different scenarios may occur. In the first one a precise numeric cut-off point after transplantation is expressed (*not until, not before*):

(15) Chronic rejection is usually not evident until at least 6 months after transplant. The pathogenesis is still unclear.

In the second scenario, the complication is associated with a risk decreasing in time, without mentioning an endpoint:

(16) Arterial hypertension (AHT) is a frequent complication in liver transplant recipients. Its prevalence varies between 50-70% in the first post-transplantation months but decreases thereafter probably due to the reduction of the immunosuppressive doses.

In the third scenario, the full span of time is expressed (e.g. a one-year period) during which the complication is most pronounced:

(17) Obesity is a very frequent complication in transplanted patients […] one year after transplantation, the period when the greatest weight gain is seen.

3.3 Timing of occurrence and diagnosis

An interesting issue is the fact that even within the subgroup of immediate complications, both the nature of the complication and its treatment depend on the moment of discovery: similar sets of symptoms may cause different kinds of pathology. This is the case, for example, for the most frequent complication in pediatric cases:

(18) Symptoms are highly variable and depend on the timing of development and diagnosis.

(19) When the thrombosis occurs at an early stage, it typically leads to ischemia/necrosis of the graft; in contrast, when it occurs at a later time point, it generally leads to biliary complications (intrahepatic biliomas and biliary stenosis) but with preservation of the graft function.

This evolutionary, dynamic nature of medical conditions needs to be taken explicitly into account in concept modelling of complications. In its earlier or later diagnostic establishment, a complication takes up different forms and therefore requires different treatment types. Consequently, in the case of thrombosis mentioned in the previous example, the therapy in the acute or late form consists of different medical actions:

(20) In the acute form, thrombolysis can be accomplished by surgical radiology. Arterial thrombectomy may be an alternative that can be done either by interventional radiology or surgical intervention. In patients where these options fail, urgent re-transplantation may be required. In the late form, treatment is mainly focused to prevent/treat biliary complications derived from the thrombosis.

Note that in the late form, treatment does not zoom in on the primary complication, but on the derived one. This example clearly shows that one complication may trigger another one. The same complication may be connected with or caused by different intentional operations, leading to these unintended side effects at different stages in post-operative care:

(21) Biliary fistula can occur initially in the first month in relation to anastomotic dehiscence secondary to technical errors or biliary tract ischemia. It is also a common complication in the third month when the T-tube is withdrawn.

A central issue in this dynamic picture is the notion of *lead time to diagnosis*: given the fact that complications constantly evolve, this time factor

contributes to variable medical decisions, taking transplantation as a starting point:

(22) The clinical picture is variable and depends on the time of development, lead time to diagnosis, and existence of a T-tube.

We finish this part of our investigation with two specific subcases of timing. First, some complications can occur both early, or emerge only late, after a so-called normal postoperative course. The following example refers to liver graft dysfunction:

(23) Dysfunction of the graft may occur in the immediate postoperative period (early dysfunction) or late during the follow-up of the patient {typically related to the recurrence of the original disease (viral hepatitis, primary biliary disease, sclerosing cholangitis, alcohol or autoimmune liver disease) or chronic rejection}.

This later complication's manifestation has a very distinct causal origin: it is overtly tied to the original disease, which urged for liver transplantation. Second, different complications (as the neurological states) sometimes occur simultaneously: the first complication is continuous *(disorientation)*, and then punctuated by episodes of the second one *(agitation and confusion)*.

(24) The most frequent neurological alterations are disorientation with episodes of agitation and confusion.

A very specific feature of generic late complications such as malignant tumor is the correlation between duration (of immunosuppression) and specific cancer subtypes *(Kaposi's sarcoma, skin tumors, carcinomas of vulva and perineum):*

(25) Although malignant tumors can appear at any time after transplantation, Kaposi's sarcoma followed by lymphoproliferative disorders are the earliest that usually develop. The later ones are skin tumors and carcinomas of the vulva and perineum.

3.4 Duration of complication: rejection from (hyper-) acute to chronic

Some complications occur either early or late. A specific case is graft rejection. An interesting time distinction in this respect is the one between hyperacute and acute. There is not only a difference in terms of time itself (hyperacute rejection occurring within minutes or hours), but also in terms of the complications' nature. The prefix *hyper-* refers as well to the severity of the rejection reaction and the fact that antibodies reject the graft in an irreversible way. Hyperacute rejection is humoral, whereas acute rejection has a cellular origin. This is the primary difference with *acute* rejection, for which drugs are available. The primary difference with the third subtype is that

(26) […] Chronic rejection generally occurs over a span of months, can be unresponsive to current therapy, and contributes to be a source of graft loss.

An interesting, yet unsolved issue is the difference between chronic and repeated acute rejection. Some studies report that acute rejection generally occurs in the first few weeks following transplantation, whereas chronic rejection "typically occurs several months to a year posttransplantation" (Batts, 1999) and requires additional more histological fine-tuning by means of liver biopsy.

Determining correct diagnosis for each of these complications is a highly complex issue, because of the many clinical parameters shared by different complications.

3.5 Frequency and prevalence

Frequency and prevalence are commonly used terms when describing the epidemiological status of a complication (Greenberg et al., 2005, chapter 2). Whereas incidence refers to the number of new cases occurring in a given period of time, prevalence indicates the actual number of cases alive either during a period or at some point in time.

The prevalence can be addressed in different ways: on average and based on variation (either within the different complications of a subtype or as a sample within the complication population). The following three examples illustrate this characterization in three progressive steps.

(27) The prevalence of technical complications is on average 26%.

(28) Arterial complications, particularly the thrombosis of the hepatic artery (prevalence ranging from 1.5 to 25%) are the most frequent ones.

(29) Hepatic artery thrombosis is a complication that develops more frequently in the pediatric population.

Apart from overall values (27-28) for the population, samples typically address age, such as children (29), specific pre-surgical diseases triggering grafting (30), and retransplant patients (31):

(30) Portal vein thrombosis is an infrequent complication with an overall prevalence of 2-3%.

(31) Globally, 20-40% of liver transplant recipients present atraumatic bone fractures; this

prevalence rises to 65% in patients transplanted due to cholestatic disease and in retransplant patients.

Typical long-term spans include mention of one and five year periods.

(32) Currently though, survival rates of over 90-95% and 70% at one year and five years post-transplantation, respectively are expected.

Prevalence spans reach from 100% to values as close as 1.5%, as in (33) and (28).

(33) Pleural leakage, predominantly on the right, is the most frequent complication with a prevalence reported to be as high as 100% in some series.

Different diagnostic criteria are used to characterize a (chronic) complication. Variable prevalence is therefore a common measure:

(34) The prevalence is variable, depending on the criterion used to define it and to the method used to assess renal function. Indeed, serum creatinine measurement may underestimate the presence of renal failure.

Particularly in late complications, an important comment on the relation between time and treatment has to be made: a complication may display decreasing prevalence over time. As mentioned before, complications are sometimes caused by immunosuppressive drugs. Since drug administration may be decreased over time, this has an impact on its frequency. Conceptually, there is again a correlation (or even causal relation) between treatment method and time, independent of a specific complication, as the two following examples (concerning hypertension and diabetes, respectively) show.

(35) Arterial hypertension (AHT) is a frequent complication in liver transplant recipients. Its prevalence varies between 50-70% in the first post-transplantation months but decreases thereafter probably due to the reduction of the immunosuppressive doses.

(36) A variable percentage of patients, 4-20% according to the series, will develop diabetes mellitus following transplantation (de novo DM). The prevalence depends on the time elapsed since transplantation and particularly on the immunosuppressive drugs. In the initial post-transplantation period, DM is very frequent, probably due to the use of high CNI and steroid doses.

Typically, measures for prevalence and risk may compare patients with complications to the healthy population (37), taking into account the moment of grafting (38) and stage of drug development.

(37) The natural history of malignant tumors in the transplant patient tends to be different from that of the normal population; they appear at an earlier age, tend to be in a more advanced stage when diagnosed, and their evolution is more aggressive, causing high mortality directly related to the tumor.

(38) Some data suggest that in patients undergoing liver transplantation in recent years, there is a higher incidence of hematological neoplasms with de novo internal neoplasms developing at earlier time-points than in those transplanted years ago.

A relevant measure and objective of PLTM management is the reduction of frequency of complications to values for the general population, as in the case of bacterial infections:

(39) After the sixth month, with the transplanted organ functioning normally and minimum immunosuppressive doses, the frequency of bacterial infections is reduced to figures similar to those of the general population and the causes are pathogenic bacteria of the community.

Liver transplantation entails serious risks. Prevalence therefore is not only coined in terms of morbidity, but also of (decreasing) global mortality.

(40) The global mortality in this early posttransplantation period is approximately 5-10%.

Particularly in retransplantation, mortality rises. Retransplantation entails two subsequent time sequences: the management of the first graft, leading to an incurable complication (such as graft rejection mentioned before) within the first 48 hours following surgery, and a second one, with reduced survival prognosis.

(41) However, if regression of the clinical situation is not observed after 24-48 hours, retransplantation must be considered as soon as possible to avoid the development of multiorgan failure, in which case the mortality associated with retransplantation is very high.

4 Conclusion

This paper proposes a first sketch of time factors as an associative relation relevant for modelling the temporal unfolding of PLTM complications. We list the time factors useful for a model of time.

1. A boundary separates peri-operative care and management of complications. Prophylaxis is

a peri-operative issue in avoiding complications [3.1], and should be integrated in the time model.

2. Early complications are tested and detected against normal states.
3. These complications are temporally decomposed in immediate and late complications [3.2]; complications, however, do not belong unequivocally to one of these.
4. Relevant time notions are the cut-off point for occurrence and
5. the time span of (early) complications.
6. A distinction is needed between underlying pathologies not affected by transplantation [see section 3.1], and diseases that may affect complications and patient prognosis.
7. There is a variable correlation between the snap/span time (Munn and Smith, 2008) line of complication occurrence and associated medical diagnostic and therapeutic actions [see section 3.3].
8. Complications take different symptomatic forms causing different pathologies and therefore require various diagnostic tools.
9. Lead time to diagnosis is an important time dimension in this respect.
10. A distinction is needed for duration in graft rejection, between a (hyper-) acute and chronic disease status (without treatment options or not) [see section 3.4].
11. Complications involve some measures [3.5] such as prevalence of morbidity and mortality.
12. Prevalence may decrease based on the reduction of immunosuppressive drugs in the long run.

Future work will develop in three directions, The two first steps expand the corpus, taking into account, first the most quoted review articles on PLTM complications after 2006 and second, for specifying such time relations, in specialized research articles. The final goal is to transform this descriptive conceptual research into a logical entity-relation model, which can be useful in the clinical decision-making process. Describing such a model is clearly beyond this exploratory paper. Time in PLTM provides the conceptual basis for modelling subsequent associative relations: causal relations (what is the consequence of which (un)intended aspects of transplantation management, against which kinds of complications and/or sets of symptoms,?), as well as instrumental relations (what therapeutic tools, such as devices, drugs, surgical techniques, are used in order to prevent, block or reduce what kind of complications?).

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